The Tasmanian Atrial Fibrillation Study: Transition to Direct Oral Anticoagulants

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A thesis submitted in fulfillment of the requirements for the degree of

Doctor of Philosophy

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DECLARATION OF ORIGINALITY

The work contained in this thesis is original and has not been previously submitted for a degree or diploma in any other education institution or University. To the best of my knowledge and belief, I declare that this thesis contains no material previously published or written by another person except where due references are made.

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May 2018

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STATEMENT OF ETHICAL CONDUCT

Data associated with this thesis abides by the international and Australian codes of human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving Tasmanian patients with atrial fibrillation was conducted under the approval of the Tasmanian Human Research Ethics Committee: approval number H0012729.

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STATEMENT OF CO-AUTHORSHIP

The thesis is organised as a sequence of papers, either published, in press or submitted. Statements of co-authorship for the papers are provided in the subsequent chapters. Due to this thesis format, some repetition particularly in the methodology, might occur across the chapters.

Described below is the list of individuals including their organisation who have contributed to the publication or preparation of the work undertaken as part of this thesis.

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PUBLICATIONS

All of the publications listed below are related to the work described in this thesis. Because of variations while providing names to journals, the first author has been described as “Alamneh EA” in the first two articles and “Endalkachew Admassie” in subsequent publications. Chapters 2 to 6 are the accepted versions of manuscripts as they appear in publication. However, minor editorial modifications were undertaken to maintain formatting consistency within the thesis.

Peer-reviewed journal publications

1. **Alamneh EA, Leanne Chalmers, Luke R. Bereznicki.** Suboptimal use of oral anticoagulants in atrial fibrillation: has the introduction of direct oral anticoagulants improved prescribing practices? A review. Am J Cardiovasc Drugs. 2016 Jun; 16 (3):183-200. doi: 10.1007/s40256-016-0161-8.

   Located in Chapter 2: Candidate was the primary author who drafted the contents and undertook the literature search and writing. Authors 1 and 2 also had significant contribution to the design, literature search, critical review and approval for submission.

2. **Alamneh EA, Leanne Chalmers, Luke R. Bereznicki.** The Tasmanian atrial fibrillation study: transition to direct oral anticoagulants 2011-2015. Cardiovasc Ther. 2017 Jun; 35 (3):e12254. doi: 10.1111/1755-5922.12254.

   Located Chapter 3: Candidate was the primary author who, in conjunction with authors 1 and 2 contributed to the study design and development. The candidate undertook data collection, analysis and drafting of the manuscript. Authors 1 and 2 provided input into the writing of the research article and approved the submission.

3. **Endalkachew Admassie, Leanne Chalmers, Luke R. Bereznicki.** Changes in oral anticoagulant prescribing for stroke prevention in patients with atrial fibrillation. Am J Cardiol. 2017 Oct; 120 (7):1133-1138. doi: 10.1016/j.amjcard.2017.06.055.

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4. **Endalkachew Admassie, Leanne Chalmers, Luke R. Bereznicki.** Thromboembolism and mortality in the Tasmanian atrial fibrillation study. J. Cardiovasc Pharmacol Ther. Apr 2018. DOI: 10.1177/1074248418769638.

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Conference abstracts

1. Endalkachew Admassie, Leanne Chalmers, Luke R Bereznicki. Antithrombotic medication use and outcome evaluation: retrospective study in Tasmanian patients with atrial fibrillation. University of Tasmania, Graduate Research Conference 2015. Hobart, September 2015.
2. Endalkachew Admassie, Leanne Chalmers, Luke R. Bereznicki. The Tasmanian atrial fibrillation study: transition to direct oral anticoagulants, 2011-2015. Australian Pharmaceutical Science Association (APSA) annual conference 2016. Sydney, Australia, 2-5 December 2016.
3. Endalkachew Admassie, Leanne Chalmers, Luke R. Bereznicki. Oral anticoagulant use in patients with atrial fibrillation: pre- vs post-direct oral anticoagulant era comparisons. European Heart Journal 2017, Volume 38, Issue suppl-1 August 2017. European Cardiology Congress 2017. Barcelona, Spain, 26-30 August 2017.
4. Endalkachew Admassie, Leanne Chalmers, Luke R. Bereznicki. Bleeding-related admissions in patients with atrial fibrillation receiving antithrombotic therapy: results from the Tasmanian atrial fibrillation (TAF) study: APSA-ASCEPT Joint Scientific Meeting: Brisbane, Queensland, Australia, 6-8 December 2017.

We the undersigned agree with the above stated “proportion of work undertaken” for each of the above published or under review peer-reviewed articles contributing to this thesis:

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ABBREVIATIONS

Acronym	Definition
ACC	**American College of Cardiology**
AF	**Atrial fibrillation**
ADR	**Adverse drug reaction**
AHA	**American Heart Association**
APT	**Antiplatelet**
AR-DRG	**Australian refined diagnosis related groups**
ARISTOTLE	**Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation**
CCI	**Charlson comorbidity index**
CI	**Confidence interval**
CCS	**Canadian Cardiovascular Society**
CHF	**Congestive heart failure**
CrCl	**Creatinine clearance**
DM	**Diabetes mellitus**

DOAC	**Direct oral anticoagulant**
DVT	**Deep venous thrombosis**
ENGAGE-AF	**Effective Anticoagulation with Factor Xa Next Generation in atrial fibrillation**
GFR	**Glomerular filtration rate**
GLORIA-AF	**Global Registry on long-term oral anti-thrombotic treatment in patients with atrial fibrillation**
GARFIELD-AF	**Global anticoagulant registry in the FIELD-atrial fibrillation**
HR	**Hazard ratio**
HRS	**Heart Rhythm Society**
HTN	**Hypertension**
ICH	**Intracranial haemorrhage**
INR	**International normalised ratio**
IQR	**Interquartile range**
IS	**Ischaemic stroke**
ISTH	**International Society of Thrombosis and Haemostasis**
MeSH	**Medical subject headings**

MI	**Myocardial infarction**
NICE	**National Institute for Health and Care Excellence**
NOAC	**Novel oral anticoagulant**
NVAF	**Non-valvular atrial fibrillation**
OAC	**Oral anticoagulant**
OR	**Odds ratio**
ORBIT-AF	**Outcomes registry for better informed treatment of atrial fibrillation**
PBS	**Pharmaceutical Benefits Scheme**
PE	**Pulmonary embolism**
PINNACLE	**Practice innovation and clinical excellence**
PREFER in AF	**PREvention of thromboembolic events in-European Registry in Atrial Fibrillation**
PY	**Person-year**
RCT	**Randomised clinical trial**
RE-LY	**Randomised Evaluation of Long-term anticoagulation therapY**
RHH	**Royal Hobart Hospital**

ROCKET-AF	**Rivaroxaban Once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for the prevention of stroke and embolism trial in atrial fibrillation**
SD	**Standard deviation**
SE	**Systemic embolism**
TAFs	**Tasmanian Atrial Fibrillation study**
TE	**Thromboembolism**
TGA	**Therapeutic goods administration**
TIA	**Transient ischaemic attack**
TSOAC	**Target specific oral anticoagulant**
TTR	**Time in therapeutic range**

ABSTRACT

Atrial fibrillation (AF) is the most common cardiac dysrhythmia in the world, mainly affecting elderly individuals. The incidence and prevalence of AF are increasing globally owing to an increase in the aging population and associated risk factors. Epidemiological data show the overall prevalence of AF to be 1.5-2%, increasing from 0.7% in people aged 55-60 years to 17.8% in those aged ≥ 85 years. AF adversely affects cardiac haemodynamics leading to thromboembolism, manifesting as ischaemic stroke/transient ischaemic attack (TIA), deep venous thrombosis, pulmonary embolism, and myocardial infarction. Patients with AF have a 5-fold increase in the risk of stroke compared to patients without AF, and about 15-20% of all strokes are due to AF. AF-related strokes are often more severe, resulting in greater disability, and higher fatality and recurrence rates than non-AF-related strokes.

Oral anticoagulant (OAC) therapy is essential for thromboprophylaxis in AF. Evidence-based AF guidelines recommend OACs for patients with additional stroke risk factors. Optimal use of OAC therapy in AF reduces the risk of stroke by about 60-70% compared to placebo. For many decades, vitamin K antagonists (VKAs) such as warfarin have been the only OACs available for long-term anticoagulation in AF. However, VKAs are limited by their narrow therapeutic window requiring frequent monitoring and dose adjustment, drug-drug interactions, and adverse drug reactions, primarily fatal and non-fatal bleeding events. These limitations have resulted in guideline discordance, poor adherence, and suboptimal patient outcomes. According to contemporary AF guidelines, the majority of patients with AF are categorised as being at high risk of stroke according to the CHA_2DS_2-VASc score (i.e. CHA_2DS_2-VASc ≥ 2) and thus eligible for OAC therapy. However, observational studies confirm widespread under-

prescribing of OACs in at-risk AF patients. Despite changes in clinical guidelines, antiplatelet (APT) agents remain commonly used for stroke prevention in AF.

The challenge of optimal anticoagulation in AF has prompted the search for “ideal OACs” that are safe, effective, and convenient to use in AF. Since 2008, four direct-acting OACs (DOACs), namely dabigatran, rivaroxaban, apixaban, and edoxaban, have been approved as alternative anticoagulants to VKAs for stroke prevention in patients with non-valvular AF (NVAF). Analysis of data from large randomised controlled trials (RCTs) has shown that DOACs have comparable efficacy, with a lower rate of major bleeding than warfarin. Moreover, DOACs are convenient for dosing, have predictable pharmacokinetics and routine monitoring is not required. With the introduction of DOACs, a new era has started resulting in a paradigm shift in the management of AF patients requiring anticoagulation. AF guidelines in most countries now recommend DOACs as first-line agents for stroke prevention in NVAF.

DOACs were launched in Australia with market approval of dabigatran in 2011. However, these agents only became widely available after being listed on the Pharmaceutical Benefits Scheme (PBS) for subsidy by the government in August 2013. At the commencement of this study, limited data was available from the Australian perspective regarding the clinical integration of DOACs, their impact on anticoagulation practices, and clinical outcomes of antithrombotic therapy in AF. The Tasmanian Atrial Fibrillation study (TAFs) was established in 2011 to generate current data pertaining to the evolving antithrombotic therapy patterns and outcomes of antithrombotic treatment in AF. The TAFs was initiated at three Tasmanian Hospitals - the Royal Hobart Hospital (RHH), Launceston General Hospital, and North West Regional Hospital. The current study was part of the TAFs, specifically focussed on patients with AF as primary or secondary diagnosis who were admitted to the RHH between 2011 and

2015, for whom long-term follow-up data were readily available. It is intended that the findings from this study could be used by practitioners to inform decision making in the management of AF, and by policymakers to analyse the impacts of the new therapies on AF care and the overall health care system.

The main objectives of the studies contained in this thesis were to: i) describe antithrombotic prescribing patterns in AF with a particular focus on the clinical integration of DOACs in the five years after they were introduced into Australian clinical practice, ii) investigate anticoagulation practices in relation to current AF guidelines before and after DOACs became widely available in Australia, iii) assess rates of, and risk factors for thrombosis and all-cause mortality in the pre- and post-DOAC eras, and iv) investigate bleeding-related hospitalisations in patients with AF who received antithrombotic therapy.

To describe antithrombotic prescribing patterns and assess the clinical integration of DOACs, we assessed patients with AF admitted to the RHH between 2011 and 2015. Digital medical records were used as the data source. Study participants were grouped into three cohorts based on the antithrombotic therapy prescribed at discharge of index admission (first admission during the study period): 1) warfarin - patients discharged with lone warfarin or warfarin-APT therapy, 2) DOAC - patients discharged with lone DOAC or DOAC-APT therapy, and 3) APT - patients prescribed lone or dual-APT therapy. Index admission dates were organised into quarterly (Q) periods, and the proportion of antithrombotic prescribing in each cohort was determined by dividing the number of patients prescribed each agent by total patients receiving antithrombotic therapy within the respective period.

In total, 3265 patient records were reviewed, of which 2390 were included in the assessment of antithrombotic prescribing patterns. Overall, participants of this study were relatively more

comorbid and had higher stroke and bleeding risk scores versus those observed in the RCTs that compared warfarin and DOACs. However, patient demographics and comorbidities in our study were broadly similar to large AF-registry data reported elsewhere. Antithrombotic agents were prescribed for the majority of our study population. DOACs accounted for 18.4% of patients receiving antithrombotic therapy in 2011-2015; the proportion of patients receiving a DOAC steadily increased from 3.9% among OAC users in Q3, 2011, to 67.6% in Q2, 2015 ($p < 0.001$). Accordingly, DOACs became the most commonly prescribed antithrombotic medications in AF soon after they became government subsidised and listed on the BPS for public use. Warfarin and APT prescribing, on the other hand, declined significantly, although a substantial proportion of patients continued to be prescribed APT therapy.

In a subsequent study to investigate OAC prescribing in relation to AF guidelines and assess the impact of the availability of DOACs on anticoagulation practices, we reviewed patients with NVAF admitted to RHH between 2011 and 2015. Based on index admission periods, patients were grouped into two cohorts: pre-DOAC era - admission before the listing of DOACs on the PBS (January 2011 to July 2013), and post-DOAC era - admissions between August 2013 and July 2015. Patients' stroke risk scores were estimated using the CHA_2DS_2-VASc method. The proportion of OAC prescribing overall, and by stroke risk stratification was compared between the two eras. Logistic regression was used to identify factors associated with OAC prescribing in the pre-DOAC, post-DOAC, and overall study periods.

In this analysis, we identified 2118 patients with NVAF (1089 vs 1029 from the pre- and post-DOAC eras, respectively). Overall, anticoagulation increased from 52.5% in the pre-DOAC to 60.7% in the post-DOAC era ($p < 0.001$). Furthermore, anticoagulation of high-risk patients (CHA_2DS_2-VASc ≥ 2) improved significantly (55.2% vs 63.1%, $p = 0.001$). In multivariate

analysis, DOAC era (OR 1.40, 95% CI 1.17-1.68) and CHA_2DS_2-VASc ≥ 2 (OR 1.95, 95% CI 1.36 - 2.80) were independent predictors of OAC prescribing in both eras and the whole study period. Conversely, increasing age and prior bleeding were inversely associated with OAC prescribing. In summary, a significant increase in OAC prescribing was observed particularly among high-risk patients in the post-DOAC era. This was likely driven by the widespread availability of DOACs, as well as updates in the AF guidelines associated with the introduction of the new agents. However, OAC underuse in high-risk and overuse in low-risk patients was apparent throughout the study period highlighting the need for further improvement.

The third study aimed to investigate the impact of DOAC availability on thromboembolic events (TEs) and all-cause mortality in patients with AF. We compared incidence rates of TEs and all-cause mortality in the pre-DOAC and post-DOAC time periods (as above). Primary outcome measures included TEs (ischaemic stroke/TIA, systemic embolic events, myocardial infarction), and all-cause mortality. Event rates were estimated by following patients with AF newly initiating antithrombotic therapy to the first TE event, treatment switch/discontinuation, death or end of study period, whichever occurred first. Cox regression analysis was used to identify risk factors associated with incident TE and all-cause mortality. Among 1125 patients newly initiated on antithrombotic agents (542 and 583 patients from the pre- and post-DOAC eras, respectively), we observed a significant decrease in the incidence rates of overall TE (rate per 100 PY, 2.2 vs 3.3, $p < 0.001$) and ischaemic stroke/TIA (1.8 vs 2.2, $p = 0.023$) in the post-DOAC era compared to the pre-DOAC era. Furthermore, the rate of all-cause mortality was significantly lower in the post-DOAC era than the pre-DOAC era (2.5 vs 3.1, $p = 0.002$). Increasing age, prior stroke, and admission in the pre-DOAC era represented risk factors for incident TE, ischaemic stroke/TIA, and mortality in this study population.

In the final analysis, to evaluate hospital admission due to bleeding, we included all AF patients who received antithrombotic treatment during the study period. Bleeding rates were estimated by following patients newly initiating thromboprophylaxis to the first bleeding event, treatment switch/discontinuation, death or end of the study period. Multivariate logistic regression was used to identify predictors of bleeding-related hospitalisation. In total, 2202 AF patients who received antithrombotic agents were included; 113 presented to the hospital with a major or minor bleeding event during a mean follow-up period of 1.8 years. The combined incidence of major and minor bleeding was significantly higher in warfarin- vs DOAC- and APT-treated patients (4.1 vs 3.0 vs 1.2 per 100 PY, respectively; $p = 0.002$). Similarly, the rate of major bleeding was higher in the warfarin group as compared to the DOAC and APT cohorts (2.4 vs 0.4 vs 0.6 per 100 PY, respectively; $p = 0.001$). Increasing age, a history of prior bleeding, and discharge antithrombotic choice of warfarin or multiple antithrombotic therapies were independently associated with bleeding events.

In summary, in this real-world cohort of the TAFs, antithrombotic prescribing in patients with AF has changed profoundly over the study period, characterised by a major shift towards the prescribing of DOACs. The availability of DOACs has been associated with a significant increase in the rates of anticoagulation. However, a large proportion of high-risk patients still receive APT therapy or remain untreated. Conversely, a substantial proportion of low-risk patients with AF receive OACs highlighting the need for further improvement. This data also suggested that TEs and all-cause mortality rates tended to decline during the post-DOAC study period when compared to the pre-DOAC era, possibly driven by the increasing anticoagulation rates and the use of DOACs in preference to warfarin. Furthermore, the rate of major bleeding and ICH, in particular, was lower in DOAC- than warfarin-treated patients. We also identified

several factors associated with thromboembolic and bleeding events that could be targeted for future intervention, notably increasing age, comorbidities (prior stroke and bleeding), and warfarin, and multiple antithrombotic prescribing. Further studies are warranted to investigate barriers to OAC prescribing, primarily among the elderly patients, including those with a history of prior bleeding; comparative effectiveness of individual DOACs; and the appropriateness and clinical outcomes of multiple antithrombotic treatments in AF.

The body of work presented in this thesis provides a number of real benefits to the various stakeholders involved in the management of AF. Policy makers will be able to better analyse impacts of the changing landscape of anticoagulation on the overall health service expenditure. Practitioners will have additional information for a more tailored approach in selecting the right treatment to the best benefit of individual patients. Our data could also be used as an input in the revision/development of local and national AF guidelines. Lastly, the findings reported in this research can be used in promoting the understanding of the various OAC options including associated risks and benefits. While the quality of stroke prevention and the outcomes of AF patients have improved in recent years, stroke prevention in AF is not yet optimal. The data presented in this thesis highlight these improvements and deficiencies in the Australian setting and can potentially be used to fully realise the benefits of OACs in the prevention of stroke associated with AF.

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CHAPTER ONE

1. INTRODUCTION

1.1 Definition and pathophysiology of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is characterised by high-frequency dyssynchronous contraction of the upper cardiac chambers (atrial excitation) associated with irregular ventricular excitation [1]. It is well understood that a focus of rapid ectopic electrical activity, often located in the muscular sleeves that extend from the left atrium into the proximal parts of pulmonary veins, plays a critical role in the initiation and propagation of AF [2]. The abnormal electrical activity in the upper cardiac chambers undergoes irregular conduction across atrioventricular node, and subsequently to the lower cardiac chambers (ventricular excitation) causing a chaotic and quivering heartbeat [1-3].

The pathophysiology of AF is thought to be multifactorial and involve a complex interaction of triggers, substrates, and autonomic influences [4].The various aetiological factors that cause a complex array of pathological changes in the atria of the heart resulting in AF include: hypertension, diabetes, heart failure, obesity, obstructive sleep apnoea, coronary artery disease , pulmonary embolism, increasing age, male sex, and genetic disorders [5,6]. Moreover, AF may be acutely associated with physiological stressors such as surgical procedures, hyperthyroidism, chronic respiratory diseases, and alcohol ingestion. All of these factors increase local ectopic electrical firing (rapid focal activity) or conduction disturbances (local re-entry) leading to AF [7].

AF can also occur in some patients without any overt structural heart diseases or identifiable risk factors, and such a condition is known as lone AF. The majority of patients with AF are asymptomatic while some patients have an awareness of rapid and irregular heartbeats, shortness of breath, fatigue, dizziness, and syncope [8].

1.2 Classification of atrial fibrillation

AF may be classified based on aetiology, i.e. depending upon whether it occurs without identifiable aetiology (lone AF), or whether it complicates other associated structural heart diseases [2]. A classification based on a temporal pattern of the arrhythmia has also been recommended by AF treatment guidelines [9,10]. According to presentation, duration, and spontaneous cardioversion or the success of pharmacological/electrical attempts to convert AF back to normal rhythm, five subtypes of AF are described (Table 1).

Table 1. Classification of atrial fibrillation subtypes.

AF pattern	Definitions
First diagnosed AF	AF that has not been diagnosed before, irrespective of the severity of symptoms or the duration of the arrhythmia.
Paroxysmal AF	Arrhythmia self-terminates spontaneously and is defined by consensus as termination within 7 days, although most cases terminate within 48 hours of onset. AF episodes that are cardioverted within 7 days are categorised under paroxysmal.
Persistent AF	Arrhythmia lasts more than 7 days, including those that are terminated by direct current or pharmacologic agents after 7 days.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt rhythm control strategy.
Permanent AF	Continuous AF in which a consensus has been reached by the patient and the physician not to try to restore normal rhythm. Restoration of normal rhythm is impossible and consensus has been reached not to undertake procedures to restore sinus rhythm.

Data are conflicting regarding the conversion rates of AF from one type to another and duration of the disease and underlying comorbidities can influence progression rates. In some patients, AF changes from paroxysmal to persistent, and subsequently to permanent forms because of atrial remodelling associated with the arrhythmia itself and other factors; permanent AF arises as the disease progresses and irreversible atrial structural changes occur over time [11,12]. A study by Proietti et al. [13] showed at one year of follow-up that 10-20% had progressed from paroxysmal to permanent AF, with higher progression rates observed in longer follow-up studies [14]. Conversely, AF may regress from persistent to paroxysmal AF, and asymptomatic

recurrences are common in patients with symptomatic AF [15]. Some observational data in patients with pacemakers also indicated that the majority of patients with paroxysmal AF remain paroxysmal [16,17].

Depending on the associated heart valve disorders, AF can also be classified into valvular AF or non-valvular AF (NVAF). Although various definitions are described in the literature, most guidelines define “valvular AF” as AF in patients with mitral stenosis or artificial heart valves (bioprosthetic or mechanical heart valves) [9,18,19]. Other valvular heart diseases such as mitral regurgitation, aortic stenosis, and aortic insufficiency in the presence of AF are all categorised as NVAF. Nevertheless, valvular AF represents a minor proportion of the overall AF population ranging from 4-30% of all patients with AF [20].

1.3 Epidemiology of atrial fibrillation

The clinical importance of AF gained greater attention in the 1990s when early population studies, including the Framingham Heart Study, revealed critical evidence regarding associated risk factors and patient outcomes [21,22]. AF is increasingly recognised as a major public health burden with the prevalence markedly increasing, particularly in the elderly population [23]. Aging is an important risk factor for AF and the incidence and prevalence of AF rise with increasing age. The prevalence of AF roughly doubles with each advancing decade of age, from 0.5% at age 50 – 59 years to about 10% in those over 80 years of age [24-26]. Observational studies have also reported that the epidemiology of AF differs between sex categories with a higher age-adjusted prevalence in males than in females [26,27]. Likewise, data from the Framingham Heart and the Cardiovascular Health studies showed higher rates of AF in men compared to women (3.8 vs 1.9 per 1000 PY in men and women, respectively) [28,29].

AF is estimated to affect more than 30 million people worldwide including 1-4% of adults in Australia, Europe, and the United States [30-32]. Despite the increased awareness and enhanced detection of AF in recent years [28], about one-third of the total AF population is asymptomatic causing a significant underestimation of the burden of AF [33]. In Australia, the number of AF-related hospitalisations tripled between 1993 and 2007, with the rate of increase surpassing those for heart failure or myocardial infarction [34]. A similar study examining the trends of hospital admissions due to AF in the United States also reported a significant increase in AF-associated hospitalisations from 2000 through 2010 [35]. However, a declining rate of AF-related mortality was also observed in this study. Overall, the prevalence of AF is expected to double in the next 50 years attributed to several factors, including the aging population, the increasing prevalence of AF risk factors, a rise in chronic cardiovascular diseases, and improved patient survival rates [23].

1.4 Mechanisms of thrombosis in atrial fibrillation

AF primarily affects cardiac haemodynamics due to the loss of atrial contraction, and the rapidity and irregularity of ventricular rates. This leads to a significant increase in the risk of ischaemic stroke, transient ischaemic attack (TIA), other systemic embolic events (deep venous thrombosis, pulmonary embolism), and myocardial infarction [36]. Therefore, thromboembolism is the most important complication of AF causing a significant risk of morbidity and mortality. Population studies reveal that AF is associated with a 5-fold increased risk of stroke or systemic embolism with an absolute risk ranging from about 1-20% per year, depending on additional risk factors [37]. Furthermore, patients with AF have a 1.5 to 2-fold greater risk of mortality than patients without AF [38,39]. Contemporary data show 20-30% of patients with IS have AF diagnosed before, during, or after the thromboembolic event [40-42].

Thrombogenesis associated with AF is not fully described. Components of the Virchow triad for thrombosis [7], involving stasis and turbulence of blood flow, endothelial dysfunction, and hypercoagulability have been implicated in the development of thromboembolic complications in AF (Figure 1). The current hypothesis is that AF mainly causes stasis of blood in the left atrial appendage leading to local thrombus formation obstructing the flow of blood through the circulatory system. A thrombus that breaks free and circulates to another location is known as an embolus [43]. An embolus traveling through blood circulation to the brain causes ischaemic stroke or TIA [44]. Immunological studies that measured the markers of coagulability have also indicated that AF confers a hypercoagulable state and endothelial dysfunction increasing the risk of stroke and other systemic embolic events [45-47].

Thrombi can form in the arterial or venous circulation with important implications on the clinical management and patient outcomes. The pathophysiology of arterial thrombi differs from that of venous thrombi, as reflected by the different ways in which they are treated. Unlike arterial thrombi which are triggered primarily by rapture of an atherosclerotic plaque that is platelet-rich, thrombi secondary to AF contain red blood cells – typical of venous thrombi that are rich in fibrin [48,49]. The abundance of fibrin relative to platelets in AF-related thrombi underlines the higher efficacy of OAC therapy that targets the coagulation cascade compared to antiplatelet (APT) agents that prevent platelet aggregation [50]. In summary, the mechanisms accounting for stroke, systemic embolic events, and myocardial infarction in AF are multiple and complex. Therefore, various factors need to be taken into account in designing therapeutic strategies in the management of patients with AF.

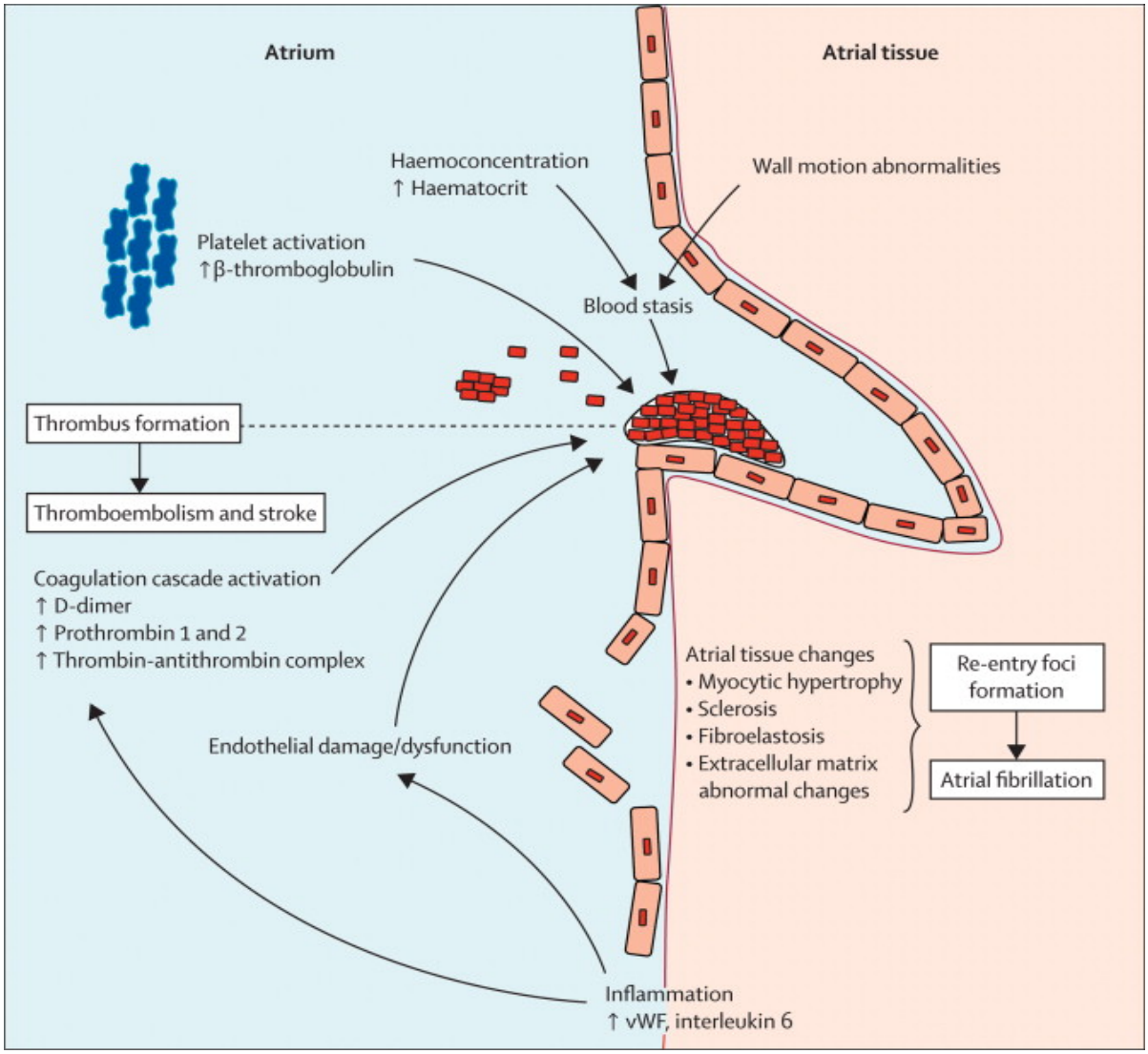


Figure 1. The major components of Virchow's triad for thrombosis in atrial fibrillation

(Source: Watson T, Shantsila E, Lip GY. Lancet. 2009; 373(9658):155-66. Reproduced with permission from Lancet.)

Note: abnormalities in the cardiac vessel wall (atrial tissue changes, endothelial damage and dysfunction), in blood flow (stasis in left atrium), and hypercoagulability (coagulation cascade activation, inflammation) contribute to thrombus formation in AF.

1.5 The coagulation cascade and targets of oral anticoagulants

The coagulation cascade is a sequence of biochemical reactions with the preceding reaction amplifying subsequent steps leading to the final stage - cross-linked fibrin strands. Coagulation proteins are the major components of the cascade involving a complex interplay of reactions leading to the conversion of soluble fibrinogen to insoluble fibrin. The fibrin strands together with the aggregation of active platelets yield stable thrombus [51,52]. Most of these proteins are inactive precursors of proteolytic enzymes known as zymogens. The activation of each component, depicted by suffix "a", requires vitamin K dependent ϒ-carboxylation of glutamic acid residues enabling them to bind calcium and facilitate the clotting process [53].

Various models of the coagulation cascade have been proposed. However, the most commonly described coagulation cascade model includes three pathways: i) the tissue factor pathway (previously called the extrinsic pathway) - is the primary activator of the cascade and involves tissue factor and factor VIIa, ii) the contact activation pathway (previously called the intrinsic pathway) - amplifies the cascade and involves factors XIIa, XIa, IXa and VIIIa, and iii) the common pathway- involves factor Xa and converts prothrombin to thrombin, which subsequently generates fibrin strands [43,51]. Figure 2 illustrates the coagulation cascade and targets of OAC agents.

The extrinsic pathway is considered as the most critical part of the cascade that is essential for haemostasis compared to the downstream pathways. Coagulation is initiated by the extrinsic pathway when tissue factor exposed at sites of vascular injury binds and activates VII. The activated VII (VIIa) activates factor X in the common pathway and generates thrombin [54]. Conversely, data from experimental studies has shown that animal models survived without the components of the intrinsic pathway. Humans deficient in factors VIII, IX, or XI

have also been observed to experience mild haemostatic defects [55,56]. Accordingly, drugs that target the upstream proteins of the cascade such as tissue factor and factor VIIa are more potent than those that target the downstream targets such as thrombin. However, inhibition of tissue factor and factor VIIa can lead to severe bleeding and the intrinsic pathways are usually targeted for drug therapy [56].

Most of the currently available OACs are designed based on targeting the downstream pathways. Whereas vitamin K antagonists (VKAs) indirectly block the syntheses of multiple components of the cascade (factors II, VII, IX, X, and anticoagulant proteins C and S), and the direct acting oral anticoagulants (DOACs) are selective inhibitors of Xa or thrombin (Figure 2) [57,58]. Emerging data also show that the contact system is essential for thrombus growth and stabilisation with factors XII and XI as potential targets for additional OACs that may be even safer than DOACs [54].

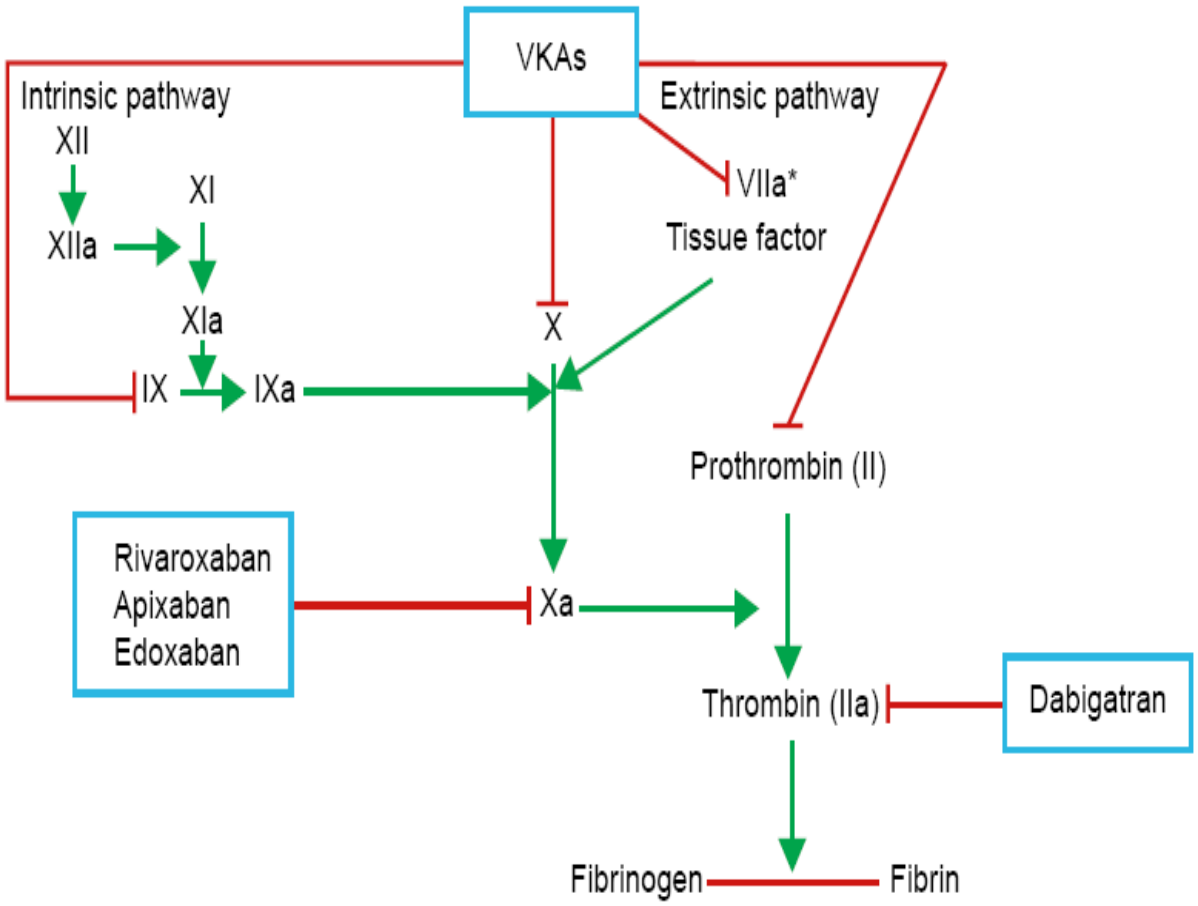


Figure 2. The coagulation cascade and targets of oral anticoagulants

(Source: Mekaj YH, et al. Therapeutics and clinical risk management. 2015;11:967-77. Reproduced with permission from Dovepress.)

* VKAs do not inhibit, but prevent the synthesis of the coagulation factors VII, II, IX and X.

Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

1.6 Clinical management of atrial fibrillation

The clinical management of AF is complex and aims to relieve symptoms, improve quality of life, and reduce the risk of thromboembolic complications and death. The overall management of patients with AF involves two major strategies: management of the arrhythmia (rate or rhythm control) and prevention of thromboembolism using antithrombotic agents (Figure 3).

The aims of a rate control strategy are to minimise AF-associated symptoms and prevent onset of heart failure (tachycardia-induced cardiomyopathy) [59]. Rate control in AF is typically achieved by pharmacological agents. Three major classes of pharmacological therapies for rate control in AF include beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin. Moreover, non-pharmacological management methods such as cardiac ablation and pacemaker implantation are also used for rate control in selected groups of patients [60].

Rhythm control restores normal sinus rhythm by means of direct current cardioversion, antiarrhythmic drugs, and catheter or surgical ablation. Pharmacological cardioversion restores sinus rhythm in about 50% of patients with recent onset AF [61-63]. Electrical cardioversion, on the other hand, restores sinus rhythm quicker and more effectively than pharmacological cardioversion [64,65]. However, antiarrhythmic agents are often used together with direct current cardioversion to help maintain sinus rhythm after the cardioversion. Various pharmacological agents are available for rhythm control in AF. The most commonly used antiarrhythmic agents in AF include Class IC antiarrhythmics (flecainide, moricizine, and propafenone), and Class III antiarrhythmic medications (amiodarone, dofetilide, dronedarone, ibutilide, and sotalol) [66].

The choice of an antiarrhythmic agent needs to be individualised depending on the relative efficacy, side effect profile, contraindications, and the patient's ventricular function. Moreover, the decision to use a rate or rhythm control strategy also requires consideration of several factors, including the degree of symptoms, the likelihood of successful cardioversion, and the presence or absence of concomitant comorbidities [67]. In patients with short paroxysms of AF, management generally focuses on controlling the arrhythmia (rhythm control). In patients

with persistent AF, however, consensus is lacking as to whether to try to restore sinus rhythm or accept the arrhythmia and control ventricular rate (rate control) [68].

Evidence shows that the risk of stroke persists in patients with additional risk factors, and the risk continues temporarily in those without additional risk factors for stroke, regardless of whether or not the arrhythmia is converted back to sinus rhythm [69-71]. Furthermore, direct current electrical and pharmacological cardioversions in patients with AF are associated with an increased risk of stroke. Patients undergoing cardioversion of AF of more than 48 hours duration represent a particularly high-risk group compared to those with AF of less than 48 hours duration. [72,73]. However, the risk of thromboembolism associated with cardioversion can be significantly reduced by using anticoagulant therapy [72,74]. Accordingly, in addition to rate and rhythm control strategies, anticoagulation is an essential component of AF management. Current AF treatment guidelines recommend that OAC therapy be commenced three weeks before cardioversion and continued for four weeks afterwards (in those without a need for long-term OAC) [9,10]. Conversely, OAC treatment should continue indefinitely in patients at increased risk of stroke.

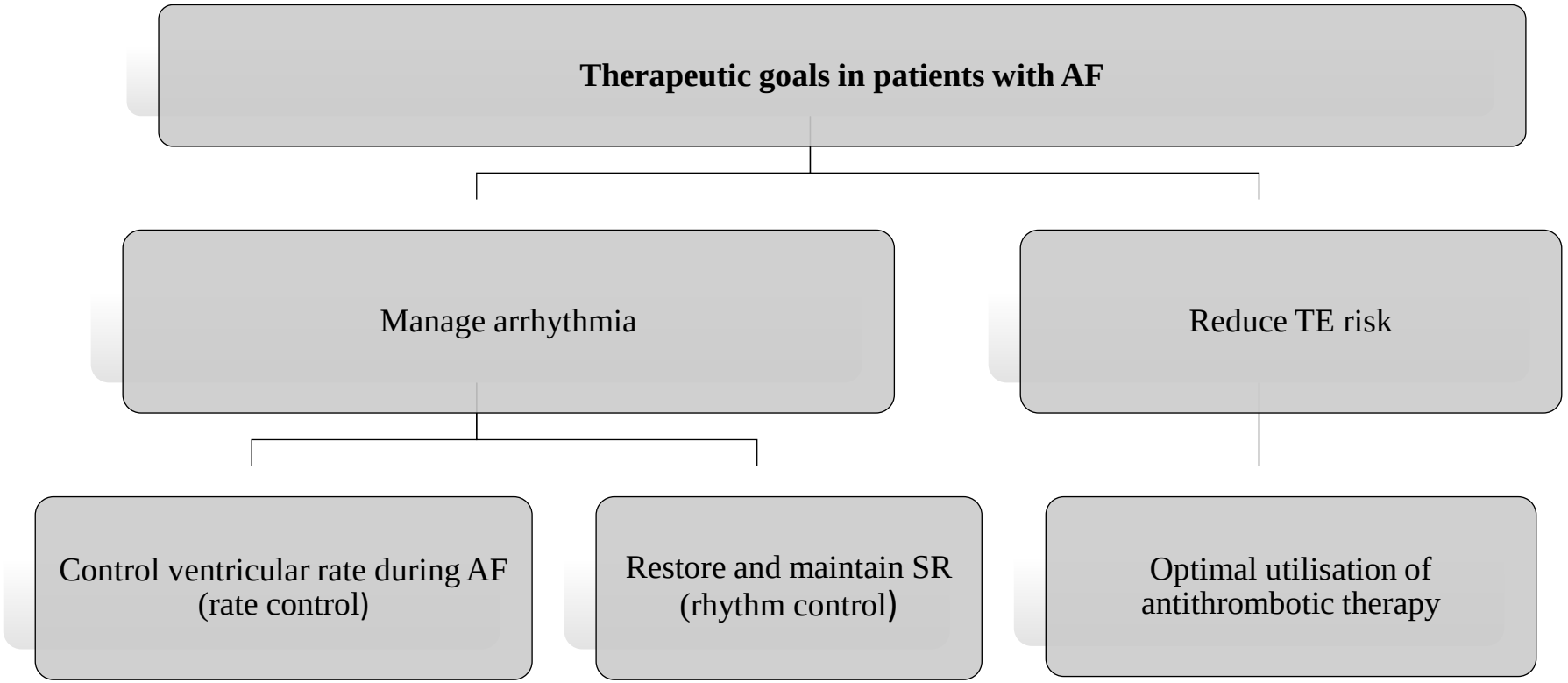


Figure 3. Therapeutic strategies in patients with atrial fibrillation.

Abbreviations: TE, thromboembolism; SR, sinus rhythm.

1.7 Antithrombotic therapies in atrial fibrillation

The risk of stroke or other systemic embolic events in AF can be significantly reduced by optimal utilisation of antithrombotic medications. Various classes of antithrombotic agents have been approved for thromboprophylaxis in AF. The major groups of antithrombotic medications used in routine clinical practice include: anticoagulants (VKAs, DOACs, low molecular weight heparin and derivatives) – block the coagulation cascade and prolong clotting time thereby reducing fibrin formation and preventing clots from growing; and APT agents (e.g. aspirin and clopidogrel) – limit migration and aggregation of platelets thereby preventing them from clumping and also prevent clots from forming and growing [75]. Most of the current AF guidelines recommend OAC therapy for stroke prevention in eligible patients with AF while some guidelines also suggest APT agents in patients with contraindications to OACs or those at intermediate risk of stroke [10,19,76].

1.7.1 Vitamin K antagonists

VKAs are a class of OACs including warfarin (coumadin), dicumarol and acenocoumarol that decrease thrombosis indirectly by inhibiting the actions of vitamin K in the coagulation cascade. Vitamin K is essential for the synthesis of multiple factors in the coagulation cascade such as factors II (thrombin), VII, IX, X, and the anticoagulant proteins C and S. Vitamin K must be regenerated from a biologically inactive epoxide by vitamin K epoxide reductase for the continued synthesis of activated clotting factors. VKAs are structural analogues of vitamin K and act as competitive and irreversible inhibitors of vitamin K epoxide reductase, inhibiting the recycling of inactive vitamin K epoxide back to an active form (Figure 4) [77,78]. In addition, VKAs have the potential to be pro-coagulant, primarily at the initial stages of therapy,

as they inhibit the carboxylation of regulatory anticoagulant proteins, C and S [79]. However, the transient pro-coagulant effect decreases over time and the anticoagulant effect of VKAs becomes dominant at the later stages of treatment when the balanced decrease of clotting factor levels is achieved.

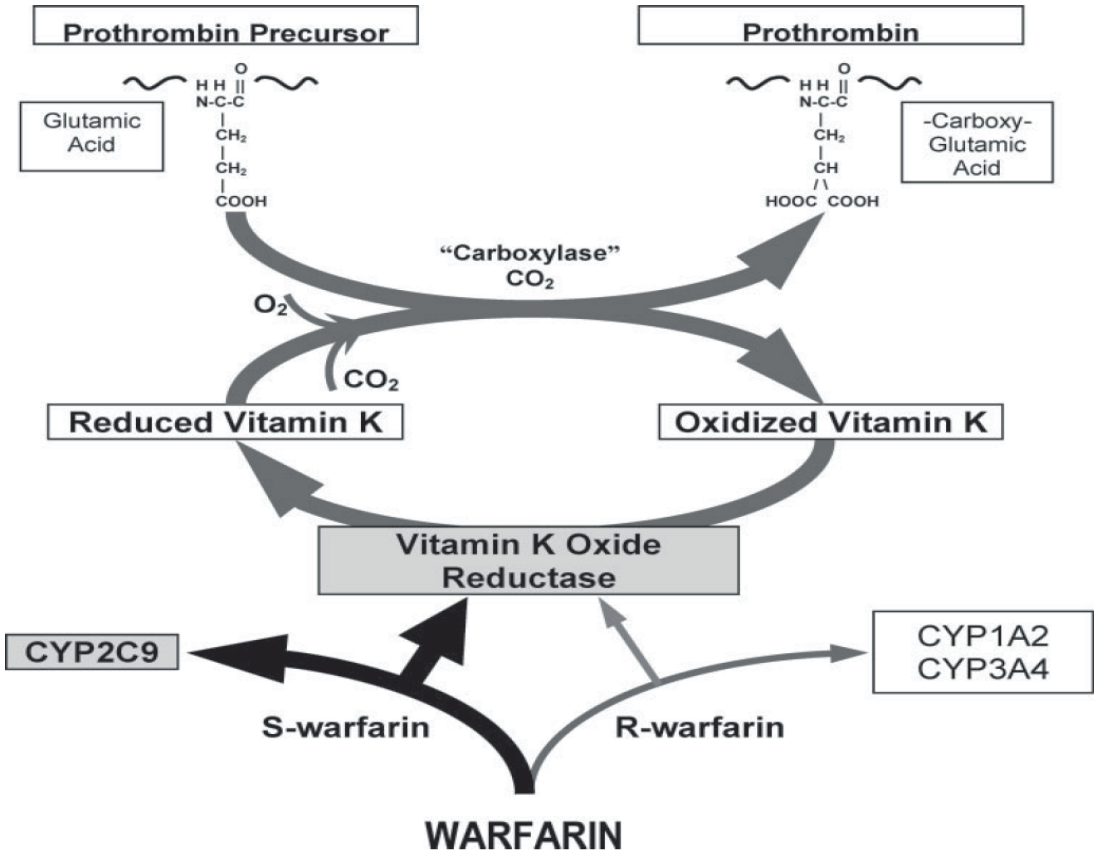


Figure 4. Recycling of oxidised vitamin K (vitamin K epoxide) to reduced vitamin K and the effect of warfarin.

(Source: Ansell J et al., Chest. 2008; 133 (6 Suppl):160s-98s. Reproduced with permission from ELSEVIER).

Note: Vitamin K epoxide reductase is an important warfarin sensitive enzyme and serves as a major target for the S enantiomer of warfarin or other VKAs. S-warfarin is metabolised by the P450 cytochrome enzymes.

"What was good for a war hero and the President of the United States must be good for all, despite being a rat poison!" **Duxbury and Poller, 2001 [80]**.

The pioneering discovery of VKAs dates back to the early 1920s when an epidemic of haemorrhagic diathesis of cattle was reported in North Dakota, the United States of America. Frank Schofield noticed that cattle bled only when they were fed mouldy sweet clover and named the ailment "sweet clover disease" [81]. The disease was reversed if the offending mouldy hay was removed or if fresh blood was transfused. In 1940, the active compound that caused "sweet clover disease", coumarin, was identified and isolated by Karl Link [82]. Coumarin was metabolised by interacting with certain fungi in the mouldy hay and changed to dicoumarol. In 1945, Karl Link was funded by the Wisconsin Alumni Research Foundation (WARF) for his continued research on dicoumarol and suggested it as a rodenticide, the rodents dying of haemorrhage. However, dicoumarol proved to be slow-acting compound. Further research on several variations of coumarin led to the development of warfarin, named after the initials of the funding company, and marketed as a rat poison in 1948 [83]. In 1955, warfarin was given to Dwight Eisenhower, the then President of the United States, after he suffered an MI, marking a successful transition from a rat poison to clinical application [80].

A number of randomised control trials conducted since the early 1960s established the safety and effectiveness of warfarin for the prevention of stroke in patients with AF [84,85]. Warfarin has been used as the gold standard and most widely prescribed OAC in AF and other embolic diseases; treatment with warfarin in AF can reduce the risk of stroke by about 60-70% versus placebo [86-88]. However, effective stroke prevention using warfarin therapy necessitates maintaining the international normalised ratio (INR) within the target range of 2-3. INRs above this range are associated with a significant bleeding risk (1-3% per patient-year (PY) and 3-8%

per PY reported in trial and observational data, respectively) [89-92]. The risk of bleeding in patients receiving warfarin is associated with several limitations of the therapy including its narrow therapeutic window, variabilities in dose-response relationship, requirement for strict INR control, and interactions with food and other medications [93,94]. These limitations have resulted in under-prescribing, poor treatment adherence, and suboptimal clinical outcomes. Observational studies have reported that a significant proportion of patients with AF did not receive optimal warfarin therapy or were given aspirin or no therapy [95]. A systematic review of 56 studies also showed the proportions of patients with AF receiving no antithrombotic therapy ranged from 4-48% and those who received APT therapy ranged from 10-56%. The rate of warfarin prescribing in this study ranged from 9-86% (median 52%) [96]. Challenges of OAC use and under-prescribing of VKAs in AF are discussed in more depth in Chapter 2.

1.7.2 Direct oral anticoagulants

DOACs are antithrombotic agents that act by inhibiting a single component of the coagulation cascade thereby exerting their anticoagulant effects (Figure 2). These medications include the direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Apart from stroke prevention in patients with NVAF, DOACs have also been approved for prophylaxis and treatment of deep venous thrombosis and pulmonary embolism. The discovery of DOACs represents a major breakthrough for stroke prevention in patients with NVAF and other embolic diseases. The new agents offer potential benefits over warfarin in that they have predictable pharmacokinetics eliminating the need for regular monitoring, convenient dosing, less drug-drug and drug-food interactions, and a reduced risk of bleeding, especially in terms of intracranial haemorrhage (ICH) [58,97]. Furthermore, while there are no antidotes to neutralise the effects of some DOACs such as factor Xa inhibitors, the rapid offset

of the anticoagulant effect due to their short half-lives may be sufficient to stop bleeding in a timely manner.

Four innovative phase three clinical trials have established that the four DOACs were at least as effective as warfarin in reducing the risk of stroke or systemic embolism [98-100]. Dabigatran (110 or 150 mg twice daily) was compared against dose-adjusted warfarin in the Randomised Evaluation of Long-term anticoagulant therapY (RE-LY) study; this was a non-inferiority trial involving 18,113 patients with AF having at least one additional risk factor for stroke [98]. The primary endpoint of stroke and systemic embolism was similar between warfarin and dabigatran 110 mg (relative risk 0.91 for dabigatran 110 mg; $p<0.001$ for non-inferiority), and lower in patients receiving dabigatran 150 mg (0.66; $p<0.001$). Dabigatran 110 mg showed lower rates of major bleeding than warfarin, but the rates were similar for the 150 mg dose. However, a higher rate of gastrointestinal bleeding was observed in patients receiving both doses of dabigatran compared with warfarin. Based on these results, dabigatran was approved as the first DOAC for stroke prevention in NVAF in Europe and in the United States of America in 2010.

In 2011, rivaroxaban became the first Xa inhibitor to be approved for the prevention of stroke and systemic embolism in NVAF. This OAC was evaluated in the ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) [99]. The ROCKET-AF trial randomised 14,264 patients with NVAF to dose-adjusted warfarin or rivaroxaban, 20 mg daily (15 mg for CrCl 30-49 mL/min). Enrolled patients were at moderate or high risk of stroke, and 55% of the participants had prior stroke or TIA. In the intention-to-treat analysis, rivaroxaban was non-inferior to warfarin for the prevention of stroke and

systemic embolism. This trial also showed no significant differences in major and non-major bleeding between rivaroxaban and warfarin, although the rates of intracranial and fatal haemorrhage were lower with rivaroxaban (hazard ratio 0.67; p=0.02)

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) non-inferiority trial compared apixaban with warfarin [100]. In this study, 18,201 patients with NVAF were randomised to dose-adjusted warfarin or apixaban 5 mg twice daily; 2.5 mg twice daily dose was given to patients with two or more of the following criteria: age $\geq$ 80 years, body weight $\leq$ 60 kg, or serum creatinine $\geq$ 1.5mg/dL. After a follow-up of 1.8 years, apixaban was superior to warfarin in reducing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. In 2012, apixaban became the second factor Xa inhibitor to be approved for stroke prevention in patients with NVAF.

Edoxaban, the third Xa inhibitor approved for stroke prevention in NVAF, was assessed in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction) trial. This OAC was also non-inferior to warfarin for the prevention of stroke, and was associated with lower rates of bleeding and mortality [101].

In summary, these randomised controlled trials have shown DOACs to be at least as efficacious as warfarin, and associated with significantly lower rates of ICH, the most feared complication of OAC treatment. A meta-analysis of these trials also reported that the new OACs were associated with a reduced risk of stroke or other systemic embolic events as well as decreased rates of all-cause mortality [102]. It is likely that the reduced mortality rates in patients treated with DOACs is largely due to the significant reduction in ICH rates. These advantages make DOACs the treatment of choice in an increasing number of patients with NVAF and other

embolic diseases. The pharmacological features of the new OACs, and their advantages and disadvantages in real-world clinical practice are discussed further in Chapter 2.

1.7.3 Antiplatelet agents

APT agents are a class of antithrombotic medications that counteract thrombus formation by inhibiting platelet adhesion and aggregation. Low dose aspirin (75 to 325 mg) has been the most commonly prescribed agent for primary and secondary prevention of stroke in AF. APT therapies are shown to be most effective for arterial clots that are composed largely of platelets as opposed to AF-related embolic strokes; cardioembolic strokes related to AF are thought to be mainly due to thrombi originating from atrial appendages [103,104]. APT therapies are widely prescribed for preventing stroke in AF, although observational and trial data suggest that any potential protection is weaker compared to OAC therapy [86,105-107].

The evidence supporting APT monotherapy for stroke prevention in AF is limited. Randomised trials have reported that treatment using aspirin and other APT agents provide only modest protection against stroke or other systemic embolic events due to AF compared to both warfarin and placebo [108-110]. Meta-analyses also show that aspirin was associated with a reduction of about 22% (95% CI: 2-39) in stroke, with a less consistent effect than OAC therapy [86,111]. Studies have shown that there appears to be a general misconception over the safety and efficacy of APT therapy in AF not only in the general public but also among health care professionals [112-115]. Consequently, APT agents are commonly prescribed to a significant proportion of at-risk patients with AF with either real or perceived contraindications to OACs [86,116,117]. However, APT therapies are not any safer than OACs, primarily in elderly patients with AF [86,108]. Evidence suggests that the risk of bleeding associated with the use

of lone or dual-APT therapy is comparable to bleeding arising from using OAC therapy [108]. Accordingly, the 2016 European Society of Cardiology and the recently published Australian AF guidelines no longer recommend APT agents for stroke prevention in AF [9,118].

1.7.4 Multiple antithrombotic prescribing in atrial fibrillation

Prescribing of multiple antithrombotic agents in the form of dual-APT or OAC-APT therapy is common in clinical practice, mainly in AF patients with additional cardiovascular diseases [119,120]. Among other factors, the most common reason for dual-APT or OAC-APT combination therapy is the coexistence of indications for both drugs, usually coronary artery disease for APT and AF for OAC therapy. The majority of patients with AF require OAC treatment and coronary heart disease coexists in 20-30% of them [20,121]. However, the efficacy and safety of dual-APT or OAC-APT combination therapy in patients having more than one indication for antithrombotic treatment is unresolved. Given the different mechanism of actions, OAC-APT combination treatment increases the risk of clinically significant bleeding. Observational data show adding a single APT drug to an OAC therapy (warfarin or DOAC) increases the risk of major bleeding by 60-80% [122]. Moreover, adding dual-APT drugs to an OAC agent increases the risk of major bleeding by about 130% compared to lone OAC therapy [123].

1.8 Stroke and bleeding risk assessment

Prescribing antithrombotic treatment for stroke prevention in AF involves a trade-off between stroke and bleeding risk. The risk of thromboembolism and bleeding in patients with AF is not homogeneous; each patient's risk depends largely on the combination of specific comorbidities. Thus, the decision to use antithrombotic therapy in AF should be based upon the net clinical

benefit for a given patient. Hence, the management of patients with AF requires assessment of stroke and bleeding risk scores and appropriate use of thromboprophylaxis.

Development of stroke risk-prediction tools in AF emerged in the 1990s involving small cohort studies; these have since been refined in larger populations. Several stroke risk-scoring methods have been developed and validated to guide treatment decisions in AF. The most commonly used risk scoring methods include: $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes, stroke (doubled)) [124], and the more recent and refined version of $CHADS_2$ i.e. CHA_2DS_2-VASc, which assigns 1 point each for congestive heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and sex category (females), and 2 points for age ≥75 years, and prior ischaemic stroke/ TIA [125]. The CHA_2-DS_2-VASc score was first incorporated in the European Society of Cardiology guideline in 2010 [126]. Currently, treatment guidelines in various countries recommend using the CHA_2DS_2-VASc scoring method for OAC prescribing in AF and it has been widely accepted in clinical practice.

Similarly, a number of bleeding risk scoring methods have been proposed, primarily in patients taking VKAs. The relatively simple HAS-BLED (hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (> 65 years), drugs/alcohol concomitantly (1 point each)) score has been demonstrated to have better predictive value than other risk prediction tools [127-129]. The HAS-BLED scoring method has also been validated in patients receiving non-warfarin anticoagulant therapy such as DOACs, as well as in AF and non-AF populations [130-132]. Stroke and bleeding scoring methods, risk stratification, and AF guideline recommendations for antithrombotic therapy are discussed further in section 2.4.

The first Australian guideline for the management of AF was recently published [118]. In this guideline, a refined stroke risk scoring method, abbreviated as CHA_2DS_2-VA, was recommended by removing female sex from the CHA_2DS_2-VASc risk score. The rationale behind this modification was that female sex alone or in the presence of one additional risk factor does not confer a sufficient or consistent increase in the risk of stroke. Furthermore, the different CHA_2DS_2-VASc threshold values for males and females when recommending an OAC could be avoided by using the new CHA_2DS_2-VA score. For high-risk patients with AF, however, the Australian recommendations for OAC prescribing are in line with 2016 European AF guidelines. During the timeframe of our study, however, there was no Australian guideline for the management of AF; clinicians used a mix of European and American guidelines from various sources which were sometimes inconsistent or unclear, mainly in terms of recommendations for the moderate risk groups. Additionally, at the commencement of this study, there was a transition from use of the $CHADS_2$ to CHA_2DS_2-VASc method. Hence, we followed current European and American AF guidelines, and the CH_2ADS_2-VASc stroke risk stratification was used to evaluate OAC prescribing practices in AF.

1.9 Rationale of the current study

AF represents an increasing public health burden in Australia. Recent population studies have shown that more than 300,000 Australians have AF and this number has been projected to increase to 600,000 by 2034 [32]. The prevalence of AF in the Australian population aged 55 years or more is estimated to be 5.4% [26,32]. In 2015, the National Heart Foundation of Australia conducted a survey of emerging issues in cardiovascular diseases to prioritise clinical conditions and develop contemporary local guidelines [133]. The major criteria for comparison include the burden of disease, existence of treatment gaps, evolving therapeutic landscape, evidence of inequity and existence of treatment guidelines. AF was identified to have highest scores in the assessment standards, and recognised as a burdensome condition with increasing prevalence, mainly in elderly individuals, and in the Aboriginal and Torres Islander population.

The Commonwealth Review of Anticoagulation Therapies in AF in 2012 reported that stroke prevention in AF required improvement [134]. This review identified a number of focus areas to be addressed in relation to assessment of patients for stroke and bleeding risk, appropriate choice of antithrombotic agents, monitoring of patients, and the need for local studies on which to base the recommendations regarding the management of AF. Furthermore, DOACs were introduced into Australian clinical practice with the market authorisation of dabigatran in 2011. Little was known about the adoption patterns and safety and effectiveness of DOACs outside the clinical trial settings. Hence, we established that there was a need for contemporary data regarding the integration of DOACs, their impacts on OAC prescribing practices, and clinical outcomes in patients with AF. Thus, the Tasmanian AF study (TAFs) was initiated in three public hospitals (the Royal Hobart Hospital (RHH), Launceston General Hospital and North

West Regional Hospital) to generate current data regarding the utilisation and outcomes of antithrombotic therapy in Tasmanian patients with AF.

AF is considered the leading cause of preventable strokes in Australia. It has also been well established that AF-related strokes can be significantly reduced by optimal use of OAC therapy. However, data from real-world clinical settings show a significant discordance between AF treatment guideline recommendations and anticoagulation practices, characterised mainly by under-prescribing and sometimes over-prescribing of OACs in AF. One nationwide study, evaluating Australian general practice, reported warfarin prescriptions in only 44% of a random sample of general practice encounters in which AF was managed [135]. Another study from the RHH reported that approximately half of the high stroke-risk patients admitted with AF and without contraindications to warfarin were receiving the therapy [136]. Moreover, despite guideline recommendation, studies have also reported that significant proportions of patients with AF receive APT agents [137-139]. Various factors have been implicated in the suboptimal anticoagulation of patients with AF. The most frequently reported barriers to OAC prescribing in AF include adverse drug reactions, drug-drug interactions, the need for monitoring and dose adjustment, advanced age, and fear of bleeding complications [140-142].

After about six decades of VKA dominance as the only OAC for stroke prevention in AF, the therapeutic spectrum for thromboprophylaxis in patients with NVAF is changing significantly. Since 2010, four DOACs, namely dabigatran, apixaban, rivaroxaban, and edoxaban, have been approved for the prevention of NVAF-related embolic events. The seminal development and approval of the new antithrombotic agents have changed stroke prevention in AF.

DOACs have been approved for stroke prevention in patients with NVAF in many regions throughout the world. In Australia, three DOACs (dabigatran, rivaroxaban and apixaban)

received marketing authorisation by the Therapeutic Goods Administration (TGA) for stroke prophylaxis in NVAF. Dabigatran was the first DOAC to be approved by the TGA in April 2011 followed by rivaroxaban in May 2012, and apixaban in April 2012. Subsequently, the new therapies were listed on the Pharmaceutical Benefits Scheme (PBS) for subsidisation by the Australian government in mid-2013 [143]. Rivaroxaban was the first DOAC to be listed on the PBS in August 2013 while both dabigatran and apixaban were listed in September 2013. Warfarin has been listed on the PBS since 1964 whereas edoxaban was not approved in Australia during our study period [143].

The major clinical trials that compared the efficacy and safety of DOACs with warfarin showed that the new OACs have comparable efficacy and superior safety [98-100]. As a group, DOACs have a rapid onset of action with more predictable pharmacokinetics than warfarin and routine monitoring is not required [144]. Given their greater convenience and improved safety, DOACs have been anticipated to address the widespread challenges of optimal anticoagulation practices in patients with NVAF and improve overall patient outcomes. At the start of this study, there was limited Australian data pertaining the integration of DOACs into clinical practice, their impact on anticoagulation practices and clinical outcomes in contemporary patients with AF.

As new treatments for patients with NVAF have already been approved, assessing shifts in prescribing patterns, investigating the impacts of the new therapies on anticoagulation practice, and evaluating treatment outcomes are deemed to be top research priorities. Early practice level studies are essential for timely interventions, including refining the use of DOACs, guideline development, professional training and awareness creation about the new OAC therapies. Our review of local observational data and large AF registry studies undertaken in various countries

has been summarised in Chapter 2. In this review, we have identified ongoing issues regarding under- and over-prescribing of OACs in AF despite the availability of DOACs.

This research was part of the TAFs involving patients admitted to the RHH and undertaken to generate current evidence regarding: overall antithrombotic prescribing practices, and adoption of DOACs, and treatment outcomes in Tasmanian patients with AF. The RHH is the largest referral centre in Tasmania; patients with major health conditions are typically admitted to this hospital, and longer-term follow-up data were most readily available for these patients. As a result, these patients' data largely reflects anticoagulation practices and patient outcomes in the state of Tasmania. It was envisaged that findings from this research could help in mapping changes in antithrombotic prescribing, enhance our understanding of anticoagulation practices, identify factors associated with OAC prescribing, investigate patient outcomes in the real-world clinical settings, and inform the need for additional intervention to improve patient outcomes.

We hypothesised that the general availability of new OACs in Australia would improve anticoagulation practices and clinical outcomes in patients with AF. Given the lack of prior Australian studies regarding adoption of DOACs, their impact on OAC prescribing and treatment outcomes in AF, this thesis focussed on two research questions, each having two specific objectives (Figure 5). The first question focused on assessing changes in the overall antithrombotic prescribing in AF over time, detailing temporal patterns of antithrombotic prescribing, clinical integration of DOACs, and the impact of the availability of DOACs on OAC prescribing practices in AF in relation to current guideline recommendations. The second question focused on evaluating efficacy and safety outcomes of antithrombotic therapy in

patients with AF, primarily comparing thromboembolism and bleeding-related readmissions of patients with AF receiving warfarin, DOAC, and APT agents.

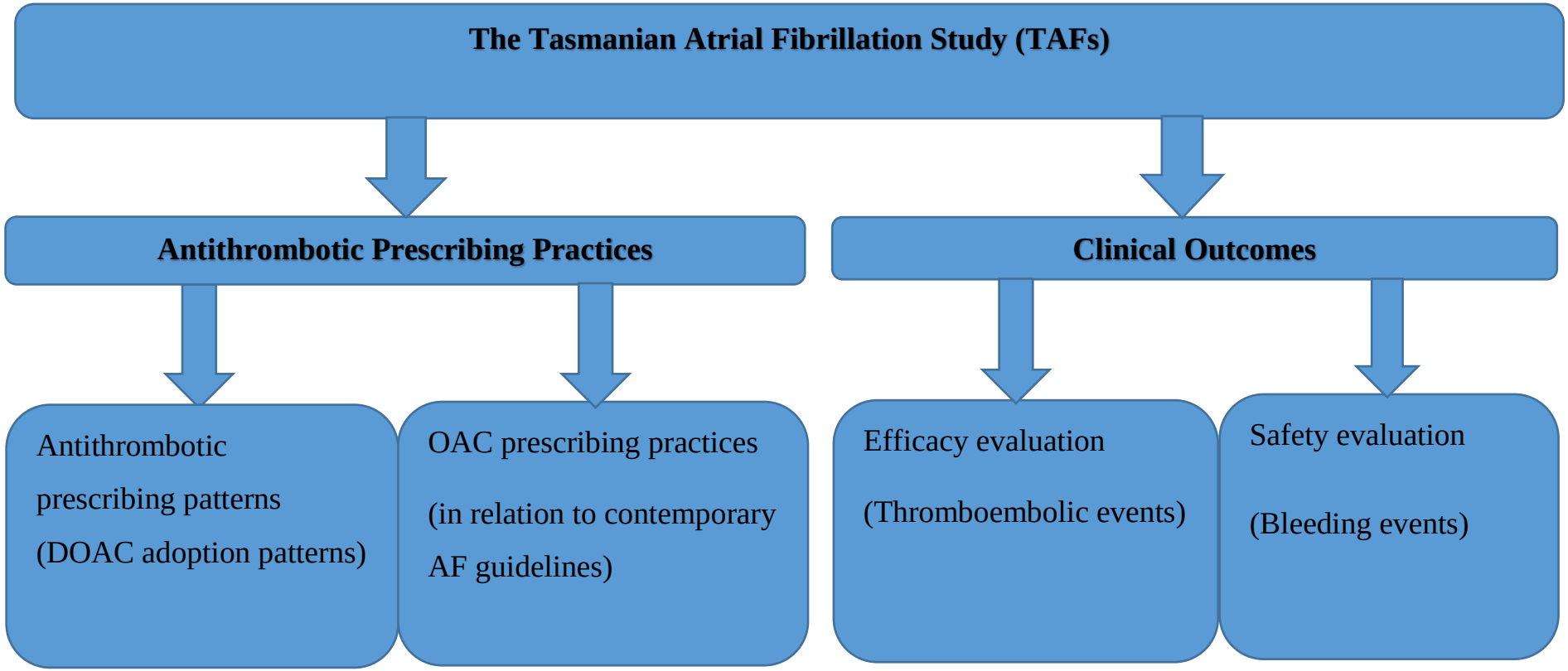


Figure 5**.** Major components of the Tasmanian Atrial Fibrillation study (TAFs).

Abbreviations: DOAC, direct oral anticoagulant; OAC, oral anticoagulant.

CHAPTER TWO

2 Suboptimal use of oral anticoagulant in atrial fibrillation: has the introduction of direct oral anticoagulants improved prescribing practices?

Overview

This chapter summarises observational data from various countries regarding suboptimal OAC prescribing, pharmacologic features and clinical integration of DOACs, and impacts of DOAC availability on OAC prescribing in AF. The results showed that the introduction of DOACs led to the revision of AF treatment guidelines and changed OAC prescribing patterns. Early evidence suggested slow integration of DOACs in most countries with limited impact on anticoagulation of patients with AF. This review was published in the *American Journal of Cardiovascular Drugs, (https://www.ncbi.nlm.nih.gov/pubmed/26862063)*, in June 2016.

2.1 Abstract

Background and objectives: Atrial fibrillation (AF) and the associated risk of stroke are emerging epidemics throughout the world. Suboptimal use of oral anticoagulants for stroke prevention has been widely reported from observational studies. In recent years, direct oral anticoagulants (DOACs) have been introduced for thromboprophylaxis. We conducted a literature review to evaluate current practices of anticoagulation in AF, pharmacologic features and adoption patterns of DOACs, their impacts on proportion of eligible patients with AF who receive OACs, persisting challenges and future prospects for optimal anticoagulation.

Literature source and selection criteria: In conducting this review, we considered the results of relevant prospective and retrospective observational studies from real world practice settings. PubMed (MEDLINE), Scopus (RIS), Google Scholar, EMBASE and Web of Science were used to source relevant literature. There were no date limitations while language was limited to English. Selection was limited to articles from peer reviewed journals and related to our topic.

Results: Most studies identified in this review indicated suboptimal use of anticoagulants is a persisting challenge despite the availability of DOACs. Underuse of oral anticoagulants is apparent particularly in patients with high risk of stroke. DOAC adoption trends are quite variable with slow integration into clinical practice reported in most countries, while there has been limited impact to date on prescribing practice.

Conclusions: Available data from clinical practice suggest that suboptimal OAC use in patients with AF and poor compliance with guidelines still remains commonplace despite transition to a new era of anticoagulation featuring DOACs.

Key points:

- The introduction of direct oral anticoagulants (DOACs) into clinical practice and updates in atrial fibrillation (AF) management guidelines have changed OAC prescribing patterns.
- Early evidence suggests slow adoption of DOACs in most countries and persisting suboptimal use of OACs in eligible patients after the introduction of DOACs into clinical practice.
- Additional DOACs and reversal agents are in the pipeline, and with ongoing efforts, optimal anticoagulation of patients with AF is an attainable goal.

2.2 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice, mainly in the aged population. The incidence and prevalence of AF have been rising over recent decades and are expected to double by 2050, partly because of the aging population and associated comorbid conditions [23,145,146]. Epidemiological studies have shown that AF affects 8-9% of people aged 80 years or more; 35% of patients with AF are > 80 years age [23,147]. The Global Burden of Diseases study reported the estimated number of individuals with AF in 2010 was 35 million. Findings from this study indicated a progressive increase in incidence, prevalence and AF-associated mortality between 1900 and 2010, with significant public health implications [148]. The overall prevalence of AF is in the range of 1-2% in developed counties, with a higher prevalence (2.5-4%) when only the adult population is considered [23,30,32]. A substantial proportion of people in developing countries are also affected by this emerging epidemic [148,149].

AF adversely impacts cardiac haemodynamics because of uncoordinated (or loss of) atrial contraction and the rapidity and irregularity of the ventricular rate [76,150]. This leads to the formation of emboli that can flow to the systemic circulation increasing the risk of ischaemic stroke. The clinical significance of AF lies in its association with a 5-fold increase in the risk of stroke. Additionally, stroke due to AF is known to be more severe and disabling than non-cardioembolic stroke and the likelihood of recurrence is higher [151-153]. AF accounts for 15 to 20% of all strokes and 36% of strokes in individuals aged > 80, of which >20% are fatal [38,154]. Hence, stroke prevention using oral anticoagulants (OACs) is considered to be a critical component of AF management in patients with additional risk factors.

Discovered in the 1920s and approved for clinical use in the 1950s, warfarin has long been the standard of care and most widely prescribed OAC throughout the world [81]. APT agents, mainly low dose aspirin, are also used widely for stroke prevention in patients who are not candidates for OACs [108,155,156]. However, APT agents are less efficacious and no safer than warfarin, primarily in the elderly. While adjusted dose warfarin reduces the risk of stroke by 64% (95% CI 49 % to 74%) and all-cause mortality by 26% compared to placebo, stroke risk reduction using APT agents is estimated to be 22% with no impact on mortality [86,151,157]. Nonetheless, optimal anticoagulation using warfarin has remained challenging due to a range of limitations including multiple interactions with drugs and food, genetic variability in metabolism and unpredictable effects [158]. Of particular concern is warfarin's narrow therapeutic index that necessitates regular monitoring and dose adjustments to maintain the INR in the range of 2-3. INR results out of this range pose significant risk. Low intensity anticoagulation (INR < 2.0) increases the risk of thrombosis while high intensity anticoagulation (INR > 3.0) increases the risk of bleeding [159,160]. Warfarin is known for common and severe adverse drug reactions. A national review of medication incidents in the United Kingdom indicated warfarin caused about 5.6% of fatal and severe drug related incidents, most of which needed hospitalisation [161].

Recently four direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban and edoxaban, have been approved for stroke prevention in NVAF, with others in late-stage clinical development. Among other benefits, DOACs offer comparable or better efficacy and safety, more predictable effects and fewer interactions with drugs and food than warfarin [162-164]. Considering their unique features and ease of use, DOACs are anticipated to address existing challenges with regard to stroke prevention in AF. However, the absence of reversal

agents for most of the new agents, issues related to cost, and lack of data and limitations to their use in certain groups of patients are considered as major challenges for their effective utilisation. This review was undertaken to evaluate the impact of DOACs on the proportion of eligible patients who receive OACs and early adoption patterns in clinical practice. Further, we discuss current practices of anticoagulation, pharmacologic features of the new agents, and persisting challenges and future prospects of optimal anticoagulation in patients with AF.

2.3 Literature source and selection criteria

This review was conducted following the PRISMA guidelines for systematic reviews. We considered the results of relevant prospective and retrospective observational studies conducted in clinical settings to assess current practices of anticoagulation in AF and adoption patterns of DOACs. Updated guidelines from different countries, randomised clinical trials, meta-analyses and review articles were reviewed to evaluate and compare clinical practice and guideline recommendations. A literature search was undertaken using PubMed (MEDLINE), Scopus (RIS), Google Scholar, EMBASE and Web of Science. There were no date limitations while language was limited to English. Selection was limited to articles from peer reviewed journals and related to our topic. Recent studies conducted on anticoagulant utilisation patterns, DOAC use in clinical practice and impacts on prescribing OACs for patients with AF were included for analysis or summary. Data reported from the reviewed articles were summarised in graphs or tables. Search terms include atrial fibrillation, prevalence, epidemiology, stroke, anticoagulation, DOACs, TSOACs, NOACs, dabigatran, rivaroxaban, apixaban, edoxaban, clinical studies, prescribing practice and warfarin. MeSH terms were included where applicable. Total abstracts identified and selected articles for this review are summarised in Table 2 below.

Table 2. Summary of literature source and selection for the review.

Total abstracts identified from PubMed using MeSH term and filters (Observational study, Meta-analysis, practice guide, randomised controlled trial: ("Anticoagulants"[Mesh]) AND "Atrial Fibrillation"[Mesh])	485
Articles obtained from other sources (Scopus, RIS), EMBASE, Web of Science, Google Scholar)	103
Articles excluded:	
Contained information not related to the objectives of this review or not published in English language	448
Articles included in this review	140
Full text articles	117
Abstracts	23
Prospective and retrospective observational studies	67
Review articles	48
Meta-analyses	8
Randomised controlled trials	9
Experimental (in vivo and in vitro studies)	2
Published AF treatment guidelines	6

2.4 Stroke risk stratification and guideline recommendations

The risk of stroke among patients with AF is heterogeneous and depends on the presence of various risk factors. Combinations of these factors have been used to formulate stroke prediction tools. The most common in use are $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/TIA - double score) and CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age > 74 - double score, Diabetes, prior Stroke, TIA or thromboembolism - double score, Vascular diseases, Age 65-74, Sex category - females single score). Recent guidelines recommend CHA_2DS_2-VASc as the preferred scoring method for it has a particular advantage in identifying low risk patients who do not need antithrombotic therapy [165,166]. Most patients categorised as moderate risk (1 point) using $CHADS_2$ score would move to 2 points in the new CHA_2DS_2-VASc score. This enables classification of patients truly at low risk and identification of more patients as eligible for anticoagulation. Treatment guidelines strongly recommend that OACs should be offered to patients with AF and stroke risk scores ≥ 2 [167-169]. While guidance currently differs on the preferred option for stroke prevention when CHA_2DS_2-VASc = 1 (for males), European guidelines recommend an OAC over single or multiple APT therapy [9].

Observational studies have shown widespread discordance between guidelines and real world practice where OACs are underused in high risk patients, and sometimes overused in low risk patients [170-172]. Since 2001, several national and international multi-centre registries have been launched to generate valuable data and assess patient characteristics, treatment patterns, implementation of guideline recommendations and treatment outcomes. The most recent registries include Global Anticoagulant Registry in the FIELD (GARFIELD) [173], Global Registry on Long-term Oral Antithrombotic Treatment in Patients with AF (GLORIA-AF)

[174], Outcomes Registry for Better Informed Treatment of AF in the United States (ORBIT-AF) [175], Acute Decompensated Heart Failure Registry (ADHERE), and PREvention oF thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF) [176]. Useful data regarding utilisation patterns, impacts of DOACs on rates of oral anticoagulation and outcomes in clinical practice are being generated from these registries and some have been summarised in Table 5. Preferred stroke and bleeding risk scoring approaches in patients with AF and antithrombotic recommendations of major treatment guidelines based on the scored values are summarised in Table 3.

Table 3. Stroke and bleeding risk scoring approaches and stroke prophylaxis recommendations in patients with atrial fibrillation [10,18,76,177].

Stroke risk scoring methods			Bleeding risk scoring method (HAS-BLED)	
Clinical parameter	CHA_2DS_2VASc (Points)	$CHADS_2$ (Points)	Clinical parameter	Points
Congestive heart failure	1	1	Hypertension or uncontrolled BP[b]	1
Hypertension (including well controlled hypertension)	1	1	Renal/liver function (one point each)[c]	1-2
Age ≥ 75	2	1	Stroke	1
Diabetes mellitus	1	1	Bleeding tendency or predisposition	1
Stroke/TIA/thromboembolism[#]	2	2	Labile INR[d]	1
Vascular diseases[a]	1	NA	Elderly (>65 years)	1
Age 65–74	1	NA	Drugs (antiplatelet agents/NSAIDs) or harmful alcohol use (one point each)[e]	1-2
Sex category, female gender	1	NA		
Maximum score	9	6		9

Guideline recommendations for stroke prophylaxis based on stroke risk scores			
Guideline	**Preferred scoring method**	**Values**	**Recommendation**
		0	No antithrombotic therapy
AHA/ACC/HRS 2014	CHA_2DS_2VASc	1	No therapy, or treatment with OAC or aspirin may be considered.
		≥ 2	OAC, either VKA or DOACs
ESC 2012	CHA_2DS_2VASc	0	No antithrombotic therapy
		1	Consider OAC for men, assess HAS-BLED score
		≥ 2	Offer OAC, assess HAS-BLED score
NICE 2014	CHA_2DS_2VASc	0 (men) or	No antithrombotic therapy
		1 (women)	
		1 (men)	Consider OAC, discuss options with patients
		≥ 2	Offer OAC, discuss options with patients

Guideline	Preferred scoring method	Value	Recommendation
CCS 2014	$CHADS_2$ (age ≥ 65 & vascular diseases are considered)	0	No therapy, but aspirin is suggested for patients aged < 65 years and with vascular disease. Female sex and vascular disease are not considered as sufficient reasons for OAC use
		≥ 1	OAC should be used including patients aged ≥ 65 years and without other risk factors.

- Interpretations: $CHADS_2$: Historically, aspirin was recommended when score = 0; aspirin or an anticoagulant could be used when score = 1, although anticoagulation was recommended; anticoagulation recommended when score was ≥ 2. Currently, anticoagulation is recommended when score is 1 or greater.
- CHA_2DS_2-VASc: People with a score = 0 (i.e. lone AF and no risk factors) do not require treatment; people with a score ≥2 should be prescribed an anticoagulant if anticoagulant therapy is not contraindicated. Recommendations differ for patients with a score = 1, and include no therapy, aspirin, dual antiplatelet therapy or an anticoagulant, depending on the risk of bleeding and patient preference.
- HAS-BLED: Score ≥3 indicates need for caution and regular review, and efforts to correct reversible risk factors for bleeding.

[a] Prior myocardial infarction, peripheral artery disease, aortic plaque. [b] Hypertension or uncontrolled BP refers to SBP >160 mmHg. [c] Abnormal renal function defined as CrCl < 50/mL/min, Scr ≥ 200 μmol/L , chronic dialysis or renal transplantation; abnormal hepatic function defined as chronic hepatic disease or evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, AST/ALT 3 times the upper limit normal). [d] < 60% TTR (an approximation of < 6 in the previous 10 INR results in the therapeutic range can be used). [e] Harmful alcohol use refers to ≥ 8 units of alcohol per week. [#]Thromboembolism included in CHA_2DS_2-VASc only.

2.5 Suboptimal oral anticoagulant use in atrial fibrillation: challenges in clinical practice

Effective stroke prevention for patients with AF requires proper utilisation of OAC therapy in eligible patients. Optimal anticoagulation is considered as a missed opportunity to impact on an important cause of stroke. Studies from clinical settings have shown underuse of OACs in eligible and overuse in ineligible patients. Underuse of OACs is noticeable, primarily in patients with high stroke risk, despite the evidence that benefit of stroke prevention outweighs bleeding risk in these populations [20,178]. Most studies conducted on utilisation of anticoagulants in AF from many countries and different practice settings have revealed one-third to one-half of eligible patients (i.e. with no contraindications) do not receive OACs.

A study on 2,578 long-term care residents (mean age, 87.0 $\pm$ 7.1 years) in 21 facilities in the state of Connecticut, United States of America, reported 53% OAC use among all ideal patients with AF identified [179]. Findings from the PINNACLE registry program in the USA (2008-2009) also reported widespread underuse of warfarin in patients with high risk of stroke. Among the 18,393 patients with non-valvular AF (NVAF) and high risk of stroke, the rate of anticoagulation using warfarin was 55.1% [180]. Preliminary results from GARFIELD indicated a disparity in risk scoring and OAC use. Data from 10,614 patents with AF in one cohort revealed 38.0% of patients from the high risk group ($CHADS_2 \geq 2$) did not receive anticoagulant therapy [173]. The Fushimi AF registry, a community based prospective study in Japan, also reported underuse of warfarin in patients with a high risk of stroke. Among the 2,914 AF patients included in this registry, only 60% with a stroke risk score of ≥ 2 and no contraindication were given an OAC [181]. A similar study from the Chinese national stroke registry reported significant underuse of warfarin in patients with AF having a high risk of

stroke and without contraindications. Of the 11,080 patients with a first ever TIA, 592 had a history of AF and only 16.2% were taking warfarin [182].

A systematic review using literature from 1997 to 2008 was undertaken to compare treatment practices of stroke prevention in AF with published guidelines. In this review, under treatment was defined as treatment of < 70 % of high-risk patients. The majority of the studies showed underutilisation of OACs in patients with high risk of stroke. Of the 29 studies involving patients with prior stroke or transient ischaemic attack (stroke risk score of $\geq$ 2), 21 of them reported OAC treatment levels below 60% [95].

OACs are not always underused. A number of studies found overuse of OACs in patients with low risk of stroke contrary to guideline recommendations. This is associated with more potential harm than benefit in patients that do not have additional risk factors for stroke. According to current guideline recommendations, patients with a CHA_2DS_2-VASc score of 0 are regarded as "truly low-risk" with a stroke/thromboembolic rate of 0.84% (95% CI, 0.65-1.08) per 100 person-years [183]. The risk of bleeding in low risk patients initiated on OAC has been shown to be higher than the risk of stroke. For example, a study in Denmark revealed that the risk of bleeding among low risk patients initiated on OAC was higher (1.08 per 100 persons at one year) than stroke rates in the untreated group (0.49 per 100 person-years) [184].

A study from the Michigan Anticoagulation Quality Improvement Initiative, (MAQI) indicated overutilisation of warfarin in patients with low risk of stroke. Among patients participating in this study, 10.4% receiving warfarin were identified as having the lowest risk of stroke (score = 0) according to their $CHADS_2$ score [185]. A prospective registry study of 3,049 AF patients presenting to cardiologists in nine European countries also revealed overutilisation of OACs in the low risk groups. Based on CHA_2DS_2-VASc, 56.4% of low risk patients were on OACs in

contrast to current European guideline recommendations [186]. The GARFIELD registry study also reported overuse of OAC; 42.5% patients with AF from the low-risk category ($CHADS_2$ = 0) received OACs. Similarly, the ADHERE international registry in Asia evaluated OAC use in 3,032 patients with AF in 10 countries. There was a significant risk-treatment mismatch between low-risk ($CHADS_2$ = 1) and high-risk ($CHADS_2$ > 2) groups. Warfarin use was 50.6% among patients with heart failure as the only risk factor ($CHADS_2$ = 1) while aspirin was used widely among patients with higher stroke risk [187].

A study from 430 general practices in the UK reported overuse of warfarin in different stroke risk groups. Thirty-seven percent of the low risk patients based on the $CHADS_2$ score, or 26.6% using CHA_2DS_2-VASc, were on warfarin. Similar evaluations from the USA Market Scan and Medicare Supplemental database found that warfarin was used in 40.1% of low risk patients [171,188].

2.6 Poor adherence to warfarin

Suboptimal adherence to warfarin places patients with AF at risk for stroke or bleeding complications. Poor patient adherence to warfarin therapy is one significant factor impacting on the quality of INR control [189]. Guidelines suggest that patients can be considered well-managed on VKA therapy if they spend at least 70% of their time in the desired INR range of 2-3 [126,190]. However, most patients receiving warfarin spend only 50% to 65% or less of their time in the range [191-193]. Success in maintaining the desired INR values can vary from country to country and treatment settings where patients are managed. Findings from the RE-LY registry in 46 countries showed a large global variation in treatment of AF and poor INR control in all regions. Mean time in therapeutic range (TTR) in this study was 62.4% in Western

Europe, and 50.9% in North America, but only between 32% and 40% in India, China, Southeast Asia and Africa [194].

Studies have shown that a considerable proportion of patients with AF interrupt therapy at least once during a mean follow-up time of about two years. These therapy gaps are shown to be significantly associated with increased risk of stroke [195-197]. A prospective study from a large contemporary cohort (2004-2011) of 71,644 patients with AF in Israel revealed low rate of persistent warfarin use based on dispensing for three months or more. The TTR among those treated with warfarin in this cohort was 42% and only 41% of the patients had a TTR >50%. On the other hand, 43% of the time was spent with an INR < 2 while 16% of time was spent with supratherapeutic INR [198]. Another study from the Fushimi AF Registry in Japan showed similar practices of warfarin under dosing and poor INR control. Among the 2,914 participants, only 54.4% maintained the optimal TTR [181]. These findings showed existing challenges with the use of warfarin and the need to improve the quality of OAC treatment.

Although some practice improvements have been observed in recent years, overall anticoagulation rates and INR control still remain suboptimal. Moreover, most observational studies have revealed that guideline recommendations regarding anticoagulant prescribing in accordance with stroke risk level are not routinely followed in clinical practice. Figure 6 summarises observational studies on anticoagulation rates in different risk groups of patients with AF based on the $CHADS_2$ or CHA_2DS_2-VASc stroke risk stratification system.

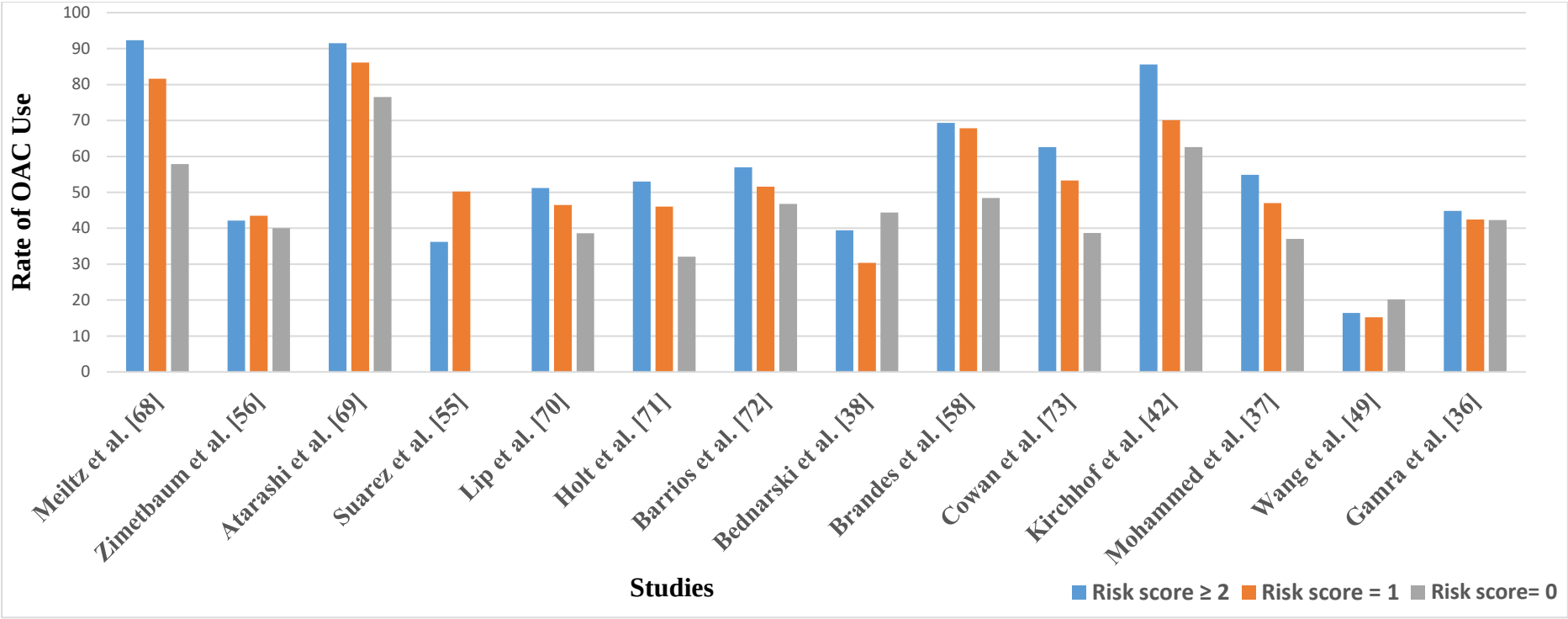


Figure 6. Summary of oral anticoagulant utilisation studies showing underuse in high risk and overuse in low risk patients with AF. [170-172,176,182,187,188,190,199-204]. AF, atrial fibrillation; CHA2DS2-VASc Congestive heart failure, Hypertension, Age [74— double score, Diabetes, prior Stroke, TIA or thromboembolism—double score, Vascular diseases, Age 65–74, Sex category—females single score, CHADS2 Congestive heart failure, Hypertension, Age C75 years, Diabetes mellitus, prior Stroke or TIA—double score, OAC oral anticoagulant, and TIA transient ischaemic attack.

2.7 Direct oral anticoagulants: pharmacologic features and advantages

The challenges of optimal anticoagulation in AF and other thromboembolic diseases prompted the search for “ideal anticoagulants” that offer the advantages of being effective, safe and more convenient to use. Progress has been achieved focusing on the two important target serine proteases in the coagulation cascade, namely thrombin (factor-II) and activated factor X (factor-Xa) [205,206].The first thrombin inhibitor to be discovered and licensed was ximelagatran. However, this agent was withdrawn from clinical practice in 2006 because of hepatic toxicity. More recently, DOACs such as dabigatran that target thrombin, and apixaban, rivaroxaban and edoxaban all targeting factor Xa have been licensed (2010, 2011, 2012 and 2015, respectively) for stroke prevention in patients with AF in the USA, Europe and other countries throughout the world [207,208].

DOACs have some unique pharmacologic features that enable easier use in patients with AF. Such features include fixed dosing, fewer drug-drug interactions and a relatively wide therapeutic window. While VKAs inhibit production of several clotting factors in the clotting cascade, the newer agents reversibly block single steps and have predictable anticoagulation effects [206]. All the four DOACs have consistent and predictable dose-response curves and time to reach steady state. Hence, haematological monitoring and dose adjustment are unnecessary. Anticoagulant effects of DOACs are determined by plasma concentration, unlike VKAs that act by blocking clotting factor synthesis. Hence, DOACs have rapid onset and offset of action making initiation and interruption considerably easier [209,210]. Although the lack of a requirement for INR monitoring is considered as an advantage, ongoing renal function tests and dose adjustments are recommended in patients with chronic kidney disease.

Accordingly, patients should be offered different dosages after assessment of renal function, age and weight.

Data from randomised clinical trials and meta-analyses have indicated that DOACs have a favourable risk-benefit profile compared to warfarin. Four pivotal clinical trials (RE-LY [98], ROCKET-AF [99], ARISTOTLE [100] and ENGAGE-AF [101]) evaluated efficacy and safety of dabigatran, rivaroxaban, apixaban and edoxaban, respectively. In these trials, DOACs were demonstrated to have equivalent or better efficacy and safety profiles compared to warfarin. Dabigatran 150 mg twice daily, apixaban 5 mg twice daily and edoxaban 60 mg once daily were more effective than warfarin. In the intention-to-treat analysis from the ENGAGE-AF trial, there was a trend favouring high-dose edoxaban in preventing stroke or systemic embolism compared to warfarin. Similarly, results from the ARISTOTLE trial showed fixed dose once daily rivaroxaban (20 mg or 15 mg daily in patients with CrCl of 30-59 ml/min) was non-inferior to warfarin in preventing stroke or systemic embolism based on analysis of the intention-to-treat trial population. Further, dabigatran 110 mg, apixaban and edoxaban were demonstrated to have better safety in terms of major bleeding rates compared to warfarin. More importantly, ICH were less with all DOACs compared to warfarin [100,105,211,212].

Insights from a meta-analysis of approved dosage forms from 50 randomised trials indicated DOACs caused significantly less major bleeding compared to VKAs (odds ratio 0.77, 95% CI, 0.64-0.91) while there was no significant difference in the rate of bleeding among the DOACs [213]. A Bayesian meta-analysis, on the other hand, revealed safety and efficacy differences among the DOACs, although all agents reduced the risk of ICH compared to warfarin. Warfarin was ranked the worst in all-cause mortality and ICH leading to the suggestion that DOACs were preferable to warfarin for patients with NVAF. Dabigatran 150 mg was the best for stroke

and systemic embolism prevention while edoxaban 30 mg was the best in terms of major and gastrointestinal (GI) bleeding events [214]. Retrospective studies also reported similar results with respect to safety and efficacy endpoint evaluations. The Danish national prescription and patient registry study indicated that VKA naïve patients initiated on warfarin therapy had a higher rate of overall bleeding compared to dabigatran group [215]. Some DOACs, however, are reported to be associated with increased GI bleeding, dyspepsia, diarrhoea and vomiting. Both meta-analysis and observational studies indicated high dose dabigatran was associated with increased GI bleeding and dyspepsia compared to warfarin [102,216]. However, such complaints are considered as minor compared to VKAs with a higher risk of drug-drug interactions and serious adverse drug reactions. These features of DOACs are anticipated to revolutionise stroke prophylaxis in patients with AF and offer significant opportunities to improve anticoagulant underuse. Pharmacodynamic and pharmacokinetic profiles of the DOACs approved for stroke prophylaxis in patients with NVAF and comparisons with warfarin are summarised in Table 4.

Table 4. Comparison of key pharmacological features of direct oral anticoagulants and warfarin for stroke prevention in atrial fibrillation [163,206,207,217-226].

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Target site and mechanism action	Vitamin-K epoxide reductase Inhibit production of II, VII, IX, X and Proteins C and S	Factor IIa - reversible inhibition of free and clot-bound thrombin	Factor Xa, Selective and reversible inhibition		
Bioavailability	> 95%	6-7%	60%	63-79%	62%
Dosage form	Tablet	Capsule	Tablet	Tablet	Tablet
Dose and dosing frequency	Variable, target INR 2-3	150mg and 110mg, (75mg for CrCl 15-30mL/min) BID	5mg (2.5mg for age ≥ 80 years, weight ≤60kg, CrCl 15-30mL/min) BID	20mg (15mg for CrCl 15-50 mL/min) OD	60 mg (30 mg for CrCl 15-50 mL/min) OD
Time to C-max	4-5 days	1-3 hours	3-4 hours	2-4 hours	1-2 hours
Half life	About 40 hours	12-15 hours	8-13 hours	5-9 hours	10-12 hours
Renal clearance	None	~80%	~25%	~66%	~49%
INR monitoring	Yes	No	No	No	No

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Prominent drug interactions	Multiple and clinically significant interactions	Interaction with strong P-gp inhibitors and inducers	Combined P-gp and CYP3A4 strong inducers, inhibitors	Potent CYP3A4, P-gp inhibitors	Strong P-gp inhibitors
Use in pregnancy	Category X, CI	CI, not established	CI, not established	CI, not established	CI, not established
Antidote	Fast reversal using PCC or FFP, slow reversal with vitamin K	Fast, complete reversal using idarucizumab	Not available [a]	Not available [a]	Not available [a]
Summary of relevant advantages (Warfarin versus DOACs)	Evaluated in all groups of patients, long experience Long half-life, once daily dosing, lower GI bleeding rates Reversible using antidotes Affordable	Rapid onset and off set of action Predictable pharmacodynamics and pharmacokinetics Lower risk of overall and ICH Minimal food and drug interactions No need of regular blood monitoring Short half-life (easier to interrupt and avoid the need of bridging during procedures)			

Abbreviations: C-max, maximum plasma concentration; CrCl, Creatinine Clearance; P-gp, P-glycoprotein; CI-Contraindicated; BID-twice daily; OD, Once daily; INR, international normalised ratio; PCC, prothrombin complex concentrate; FFP, Fresh Frozen Plasma. [a] Reversal agents in late-stage clinical development [e.g., andexanet alfa and ciraparantag (aripazine/PER977)]

2.8 Direct oral anticoagulants in clinical practice

2.8.1 Adoption patterns

DOAC approval for use in NVAF is quite recent. These agents are included in guidelines as preferred agents or alternatives to VKAs for stroke prevention in AF and are widely available in the developed world. In developing countries, however, availability of DOACs is considered to be limited [227]. Accordingly, OAC utilisation patterns in patients with AF are changing with variable proportions of DOAC use reported from different countries. Most studies reported slow integration of the new agents into clinical practice, while some revealed fast adoption patterns. Among other factors, differences in time trends of regulatory approval of countries, acceptability by patients and health care professionals and costs of DOACs are considered to be responsible for these differences.

A prospective survey of 3,049 patients with AF in the PREFER-AF registry illustrated an increasing trend of DOAC adoption in nine European Society of Cardiology member countries. Substantial inter-country differences were noted, with higher adoption of DOACs in France, Austria, Germany, Spain and Switzerland than in the United Kingdom and Italy. A high rate of OAC use was reported, 80% of patients overall, most often VKAs (71.6%), with DOACs accounting for 8.4%. Of note, the study was conducted while the new agents were not extensively available in all countries. APT therapy was still used in one-third of the patients and no antithrombotic treatment in only 4.8% [186]. This survey concluded that uptake of oral anticoagulation, mostly VKA therapy, had improved compared to prescribing a decade ago. However, APT therapy was still commonly prescribed and elderly patients continued to be commonly under-treated. Similarly, recent data from the GLORIA-AF global registry showed

a high proportion of OAC use (80% overall) in patients with AF. Unlike the PREFER-AF study, remarkable uptake of DOACs (47.7% DOACs and 32.3% VKAs) has been reported, particularly in North America and Europe [228]. A population-based descriptive analysis in Canada also reported rapid uptake of DOACs within two years of approval. The study was conducted from October 2010 to September 2012 for all OACs. Over the 24-months, prescriptions for DOACs rose more than 20-fold, to represent 21.1% of all prescriptions by the end of the period. Conversely, the rate of prescription of warfarin declined from 1,526 to 1,316 per 100,000 people ($p = 0.007$) [229].

The utilisation pattern of dabigatran was evaluated from June 2010 to August 2011 in the USA in patients enrolled in the ORBIT-AF registry. Results revealed that 12% of the 9,974 participants were treated with dabigatran and 8% had dabigatran initiated during follow-up. In contrast to the findings of the Canadian study, patients receiving dabigatran were younger (median age 72 versus 75 years, $p<0.0001$) and less likely to have prior cardiovascular diseases (4% versus 33%, $p<0.0001$). More than half of the patients with severe kidney disease were not prescribed a reduced dose, while 10% with preserved renal function received lower dosing, showing disparity with guideline recommendations [230]. Similarly, a prospective survey in Europe (EORP-AF) revealed that the rate of OAC use has increased recently, although the proportion of patients taking DOACs was found to be lower than expected. Findings from this study indicated compliance with treatment guidelines in patients from low and high-risk groups remained suboptimal. Of the 3,119 patients enrolled, the majority received VKA therapy (71.6%) whilst DOACs were used in a minority (8.4%). OACs were more often prescribed in females, and less often associated with valvular heart disease, heart failure and diabetes. DOAC use was more often associated with previous TIA and a rhythm control strategy [186].

Another study using prescription claims data from a large American medical insurance company revealed rapid adoption of DOACs into clinical practice. Conducted from 2010- 2013 on a cohort of 6,893 patients with AF initiated on OACs, DOACs accounted for 62% of new prescriptions, higher than reports from the ORBIT-AF study. DOAC initiators tended to be younger and healthier with significantly lower $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores compared to those on warfarin [231]. Some studies, however, showed greater benefits of DOACs in patients at high baseline stroke risk. The Danish National Patient Registry data revealed dabigatran, rivaroxaban and apixaban appeared superior for net clinical benefit than warfarin in warfarin in patients with CHA_2DS_2-VASc $\geq$ 2 regardless of risk of bleeding[232].

A higher rate of overall OAC use and higher DOAC adoption was also reported from a study in France. Among the 293 elderly patients aged over 75 years included in this study, 74.7% received OACs with DOACs accounting for 14.3% of the overall use. The rate of anticoagulation (VKA or DOACs) decreased moderately with age: 81.5% in the 75-79 year age group, 75% among those aged 80-84 years and 67% after 85 years [233].

2.8.2 Impacts of direct oral anticoagulants on prescribing practice

The availability of DOACs, coupled with improved stroke and bleeding risk assessment in recent treatment guidelines, is anticipated to increase the proportion of eligible patients with AF who receive thromboprophylaxis. Accordingly, studies with contrasting results on prescribing patterns of OACs and impacts of DOACs in clinical practice are emerging. Most of these studies, however, revealed under treatment of patients with AF continued to be a persisting challenge despite a transition to a new era of anticoagulation featuring DOACs.

The overall rate of anticoagulation remained unchanged, at approximately 40% after approval of dabigatran in 2010 according to a study on patterns of OAC use in the USA. This was despite rapid adoption of dabigatran during the study period. APT use as mono-therapy remained constant at roughly 4.6% of AF treatment visits. Dabigatran use increased from 0.062 million quarterly visits (2010Q4) to 0.363 million visits (2011Q4), reflecting an increased share of OAC visits [234]. A similar retrospective cohort study conducted on 183,450 patients with AF in the USA also showed a limited impact of DOACs on anticoagulation practice. The study was conducted from January 2006 to July 2012 to evaluate trends in OAC use after the introduction of DOACs. Results indicated that the proportion of patients prescribed OAC slightly increased in the post-DOAC period compared to the pre-DOAC period (33.7% versus 31.7%). However, the overall rate of anticoagulant use still remained low [235]. Similarly, findings from the PINNACLE-AF registry showed no significant change in the overall rate of anticoagulant prescribing ($p=0.43$) following approval of the DOACs. Nonetheless, there was a significant trend towards using DOACs, while the rate of warfarin use decreased over time ($p < 0.001$) [236] .

Preliminary data from Cohort 1 GARFIELD-AF registry also showed the proportion of patients receiving any anticoagulant to be suboptimal despite availability of the DOACs. One-year results from 351 Australian participants in this registry revealed suboptimal use of OAC in patients with high risk of stroke. While the average CHA_2DS_2-VASc score was 3.4, VKA and DOAC use was 59% and 4%, respectively. On the other hand, APT therapy was used in 24% of high risk patients implying continued under-anticoagulation and discordance with guideline recommendations [237]. Utilisation pattern evaluation of 19,730 incident patients with NVAF in the USA also revealed a low rate of anticoagulation since the introduction of the DOACs.

Data from medical records in this assessment showed that over 60% of newly diagnosed cases did not receive OACs despite being at high risk of stroke ($CHADS_2 \geq 2$) [238].

Physician or patients' hesitance to change treatment, preference for warfarin given extensive experience with its use, and medication costs have been shown as potential reasons for the slow uptake rate of DOACs in clinical practice and limited impacts on practice [231,239]. Moreover, DOACs require careful patient selection when considering switching from warfarin. Patients with severe renal insufficiency will have limited potential to use the new agents due to their renal excretion. Fear of bleeding and absence of reversal agents for most DOACs are also considered to be factors associated with their slow adoption into clinical practice. Additionally, there is insufficient knowledge regarding the long-term effects these agents could have on patients [240]. Accordingly, most guidelines recommend that patients on dose adjusted warfarin and with stable INR values be maintained on this therapy [9,10,18].

Overall, early evidence has suggested that integration of DOACs into clinical practice has been variable with low rates of use in most countries. Moreover, impacts of the new agents on the proportion of eligible patients with AF receiving OAC has been relatively minor in many countries. However, change is expected with time considering the fact that these agents have only been approved recently and new DOACs with improved profiles as well as reversal agents are in the pipeline. Recent observational studies on overall OAC utilisation patterns in patients with AF, DOAC adoption trends and impacts on clinical practice are summarised in Table 5.

Table 5. Summary of oral anticoagulant utilisation patterns in patients with atrial fibrillation, direct oral anticoagulant adoption trends and impacts on prescribing practice.

Research group, year and study description	**DOACs**	**VKAs**	**Summary of findings, impacts of DOACs on prescribing practice**
Huisman MV, et al **[228]**, *Am J Med. 2015* Baseline data from GLORIA-AF Phase II Registry, 10,000 patients with AF from around the world	47.7%	32.3%	Overall DOAC use was higher than VKA use High proportion of OAC use in Europe and North America Impact of DOACs on practice was not assessed
Lauffenburger JC, et al **[241]**, *Am J Cardiol. 2015* USA database of commercial Medicare claims October 2010 to December 2012. 70, 498 patients initiated on OAC for AF	37.8 %	62.2 %	High proportion of patients initiated on DOACs Patients with CHA_2DS_2-VASc score ≥2 were less likely to be on DOACs Impact on practice was not evaluated
Olesen JB, et al **[242]**; *Europace 2015* Danish nationwide descriptive study (2011-2013) 18 611 OAC-naive AF patients	46.8%	53.2%	Rapid adoption of DOACs for NVAF DOACs were used according to guidelines Impact on overall prescribing was not evaluated

Research group, year and study description	DOACs	VKAs	Summary of findings, impacts of DOACs on prescribing practice
Desai NR, et al **[231]**; *Am J Med.2014*	42.2%	57.7%	Rapid adoption of DOACs in low stroke risk groups
Medical prescription claims data, USA, 2010 2013.			Significant decline of warfarin prescribing over the study period
6,893 patients newly initiated on OACs			Impact of DOACs on practice was not explicitly stated
Shah N, et al **[236]**; *J Am Coll Cardiol.2014*.	12.9%	44.8%	Rapid adoption of DOACs, decreased use of VKAs
PINNACLE-AF outpatient registry, 2009-2012, USA			55.7% overall OAC prescribing for eligible patients
Quarter 2, 2012 results			The new agents had no significant impact on OAC prescribing
Hamilton M, et al **[238]**; *Circulation.2012*	5.5%	31.0%	Only 36.5% patients with AF initiated on OAC therapy
Incident cases of NVAF from medical records, USA			Over 60% of newly diagnosed patients did not receive OAC
19,730 patients, November 2010 to August 2011			DOAC approval has shown no impact on prescribing practice

Research group, year and study description	DOACs	VKAs	Summary of findings, impacts of DOACs on prescribing practice
Lip GY, et al **[186]** ; *Europace 2014*	8.4%	71.6%	OAC use improved compared to previous reports
EORP-AF Pilot Survey			Based on CHA_2DS_2-VASc score 80.5% received OACs
Prospective survey in 9 European countries,			Adoption of DOACs was found to be low
February 2012 to March 2013, 3,049 AF patients			Compliance with guidelines was suboptimal in low risk patients
J Steinberg BA, et al **[230]**; *J Am Heart Assoc. 2013*	12%,	---	Dabigatran was initiated in 8% during follow-up
ORBIT-AF registry in the USA			Patient education resulted in significant switching to DOACs
June 2010-August 2011, 9,974 AF patients			Study suggested cautious early uptake of dabigatran
Kakkar AK, et al, **[243]**; *PLoS One 2013.*	4%,	58%	67% of all AF patients eligible for DOACs were prescribed therapy
Perspectives from the GARFIELD registry			Higher OAC use in patients with high stroke risk
Findings from 19 countries, 10,614 AF patients			No apparent improvement in adherence with guidelines

Research group, year and study description	DOACs	VKAs	Summary of findings, impacts of DOACs on prescribing practice
Xu Y et al **[229]**; *CAMJ Open. 2013.* Data from province-wide prescription volumes, Ontario, October 2010 to September 2012	21.2%	78.9%	Impact on overall practice was not assessed Dabigatran uptake was rapid Prescription of DOACs increased by 20 fold
Sorensen R, et al **[244]**; *BMJ Open 2013.* Danish nationwide register study Prescription claims, August 22-Deember 31, 2011.	5.2%	94.8%	Overall impact was not evaluated Dabigatran uptake was rapid during the initial 4 months Most DOACs users were new initiators, good guideline compliance
Kirley K, et al **[234]**; *Circ Cardiovasc Qual Outcomes 2012.* National Trends in OAC Use in USA, 2007 – 2011 Data- IMS Health National Disease Therapeutic Index	19% total market share	------	Rate of anticoagulation remained at 40% Dabigatran rapidly adopted mainly for AF and for off-label use No impact on overall anticoagulation rates

Research group, year and study description	DOACs	VKAs	Summary of findings, impacts of DOACs on prescribing practice
Sorea C, et al **[233]**; *Archives of Cardiovascular Diseases Supplements 2014.* Retrospective study, 293 patients aged over 75 years	14.3%	60.4%	Overall rate of anticoagulation was 74.7% High proportion of anticoagulation was reported Impact of DOACs on prescribing practice was not evaluated
Kirchhof P, et al **[176]**; *Europace 2014.* PREFER AF registry in 7 European countries January 2012 to January 2013 7,243 patients with AF enrolled in the registry	6.1%	66.3%	Majority of patients (>80%) were given OACs Guidelines were followed and treatment patterns changed Percentage of patients on DOACs doubled from 6.1% to 12.6% Use of VKAs and APTs reduced in the same period.
Gorczyca-Michta, et al **[245]**; *Kardiol Pol. 2015* Prospective study on 550 patients with NVAF September2012-August 2013	19.4%	80.6%	Rate of OAC utilisation was high (84.2%) Impact of DOACs on OAC prescribing rate was not evaluated Patients treated with DOACs were older than patients on VKAs

Research group, year and study description	DOACs	VKAs	Summary of findings, impacts of DOACs on prescribing practice
Lauffenburger JC, et al **[246]**; *Am J Cardiol, 2015.* Us database of commercial and Medicare claims 70,498 NVAF patients initiated on anticoagulation	29.9% 7.9%	62.2%	Impact on practice was not evaluated Patients with high stroke and bleeding risk were less likely to be initiated on DOACs
Akao M, et al **[181]**; *Circ J 2014.* The Fushimi AF Registry, Japan 2,914 AF patients enrolled by October 2012	6.3%	48.4%	Overall OAC use was 54.6% Status of OAC use at one year follow-up did not change substantially despite DOACs availability

Abbreviations: **NVAF, non-valvular AF; OAC, oral anticoagulant;** DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; APT, antiplatelet; TIA, transient ischaemic attack

2.9 Persisting challenges and future prospects

While DOACs present an opportunity to improve stroke prevention in AF, there are still several limitations that affect their wider acceptance. To be considered as first choice in AF, DOACs must not only be more convenient but also need to result in better clinical outcomes, at an acceptable cost, with consistency in all groups of patients. Major uncertainties related to DOACs include medication adherence and persistence, absence of specific antidote for most of the DOACs, higher cost, and lack of data in some groups of patients in which they have not been adequately studied. These patients include those with mechanical heart valves, pregnancy or disease states in which there is potential for toxicity, such as renal insufficiency [247,248].

Clinical experience with DOACs is relatively short-lived and there is a lack of data from real world practice settings regarding long-term adherence and persistence with these agents. However, there are some concerns that patients may have difficulty in remembering to take DOACs without the requirement of blood monitoring [249]. Consequently, if DOACs are not taken regularly, the risk of embolic stroke may be higher as these agents have short half-lives compared to warfarin. The safety of DOACs has been challenged as there is no reversal agent for the Xa inhibitors currently approved in clinical practice. Lack of a specific reversal agent has been a major concern among prescribers and patients, ultimately affecting adoption into clinical practice [250]. Nonetheless, withholding the drug and providing supportive care indirectly achieve DOAC reversal. Compared to warfarin, the shorter half-lives of DOACs result in rapid waning of anticoagulant effect upon cessation of treatment [251,252]. Moreover, there are ongoing efforts to develop specific antidotes for DOACs. Recently, a breakthrough has been achieved with the development of a reversal agent for dabigatran. The monoclonal antibody idarucizumab binds dabigatran with a stronger affinity, 350 times higher than

thrombin. It has been tested in clinical trials and granted approval for dabigatran reversal by the FDA [253-255]. Further, a recombinant protein acting as a universal antidote for factor Xa inhibitors (andexanet alfa) is under development [256]. Approval of these agents is expected to increase the acceptance rate of DOACs and subsequently improve the practice of stroke prevention in AF.

Cost is the other challenge hindering adoption of DOACs. The direct medication cost of the new agents is much higher than warfarin. A quality and cost implications study conducted in 6893 patients with AF in the USA indicated higher patient and insurer spending for DOACs compared to warfarin users, indicating a high health care cost burden for the new agents [231]. Moreover, DOACs are taken chronically in NVAF, the disease is highly prevalent, and hence there could be a significant financial burden both on the patient and the health care system [257,258]. However, studies applying different economic models in real world practice settings have revealed dabigatran to be as, or more cost effective than warfarin. Event specific cost analysis based on efficacy and safety endpoints has showed an overall cost reduction for DOACs compared to warfarin [259-261]. Overall, issues associated with cost are considered to be transitory as more DOACs are licensed increasing the generic options.

A lack of data in some patient groups and disease states are other factors impeding adoption of DOACs into clinical practice. Clinical trials are usually performed in selected patient cohorts due to strict regulatory controls. Typically excluded in the evaluation of DOACs are those patients with advanced renal and liver dysfunctions, children, patients at extremes of body weight and with complex disease and multiple morbidities [240]. Moreover, the efficacy of DOACs, particularly dabigatran, is shown to be inferior compared to warfarin in patients with mechanical heart valves or hemodynamically significant valvular heart disease [262]. DOACs

are also not suitable in patients with history of GI bleeding while warfarin may be used with caution in these patients [225,263]. Hence, more information is needed regarding the use of DOACs in these comorbidities and special populations.

On the other hand, the new agents are approved for venous thromboembolism in some countries including Europe, USA, Canada and Japan [206]. Moreover, clinical trials are being undertaken to evaluate the safety and efficacy of DOACs for valvular AF, acute coronary syndrome and in patients with prosthetic heart valves [262,264]. Research is also currently ongoing to develop additional DOACs targeting specific steps in the coagulation process with improved pharmacological profiles [265]. Accordingly, it is likely that the options and the range of indications for DOACs will increase over time. All of these efforts are paving the way and in the future, it seems that optimal anticoagulation and stroke prevention in AF are attainable goals. However, much effort will be required in real world practice settings to refine their use and ultimately gain wider acceptance with a subsequent impact on clinical practice.

2.10 Conclusions

Current research indicates that introduction of DOACs with some pharmacological advantages has led to a revision of previous guidelines and changed prescribing patterns. Adoption trends are quite variable with slow integration of DOACs into clinical practice reported in most countries, while there has been limited impact to date on prescribing practices. Accordingly, suboptimal OAC use and poor compliance with guidelines still remains commonplace despite a transition to a new era of anticoagulation using DOACs.

Hence, it is imperative that more work is done on effective implementation of evidence-based best practice, including the selection of suitable patients for anticoagulation and their optimal

management in line with current treatment guidelines. Interventions should focus on education about recent developments regarding DOACs and reversal agents, including updates on AF treatment guidelines. Treatment guideline recommendations should be communicated effectively among health professionals to impact prescribing practices and improve OAC utilisation.

CHAPTER THREE

3 The Tasmanian atrial fibrillation study: transition to direct oral anticoagulants, 2011-2015.

Overview

This study was undertaken to address the first objective of the thesis. It describes temporal patterns of overall antithrombotic prescribing and adoption of DOACs for stroke prevention in AF. Antithrombotic prescribing patterns were assessed by organising admissions into quarterly periods. The proportions of patients receiving warfarin, DOACs, and APT agents in the corresponding quarters were determined. The results showed that DOACs became the most commonly prescribed class of antithrombotic agents in AF shortly after they were listed on the PBS. Warfarin and APT prescribing declined significantly, although a substantial proportion of patients with AF continued to be prescribed APT therapy. This study was published in the journal of Cardiovascular Therapeutics (https://www.ncbi.nlm.nih.gov/pubmed/28177198) in June 2017.

3.1 Abstract

Introduction: Contemporary Australian data regarding antithrombotic prescribing patterns following approval of direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) are limited.

Aim: The aim of the present study was to assess antithrombotic prescribing patterns before, during, and after the clinical introduction of DOACs.

Methods: Using digital medical records, this retrospective cohort study included all patients with AF as a primary or secondary diagnosis who were admitted to the Royal Hobart Hospital, Tasmania, Australia, between January 2011 and July 2015.

Results: Antithrombotic agents were prescribed for 2078 (91.9%) of 2261 patients without documented contraindication to therapy. Higher rates of OAC prescribing were observed following Government subsidisation of DOACs in Quarter 3 (Q3) 2013 than anticoagulation rates in the prior quarters, (54.4% in Q3, 2013 to 68.1% in Q2, 2015, $p < 0.001$), with the prescribing of warfarin and APT agents declining. DOACs, as a class, accounted for 18.4% of patients on antithrombotic therapy in 2011-2015; the proportion of patients receiving a DOAC steadily increased from 3.9% among OAC users in Q3, 2011 to 67.6% in Q2, 2015 ($p < 0.001$). In a sub-set of patients with newly diagnosed AF, patients commenced on DOACs were younger (70.4 vs. 73.8 years, $p = 0.04$) and had lower stroke and bleeding risk scores (CHA_2DS_2-VASc 2.8 vs. 3.3, $p = 0.03$, HAS-BLED 2 vs. 3, $p = 0.04$) than patients who were newly prescribed warfarin.

Conclusions: DOACs rapidly became the most commonly prescribed class of antithrombotic medications in patients with AF, soon after they became widely available. Warfarin and APT prescribing declined significantly, although a substantial proportion of patients continued to be prescribed APT therapy. Patients who were initiated on DOACs were typically younger with fewer comorbid conditions compared to those initiated on warfarin therapy.

Keywords

Atrial fibrillation, direct oral anticoagulants, warfarin, antiplatelet agents

3.2 Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia, mainly affecting the aged population [147]. AF is associated with a 5-fold increase in the risk of stroke across all age groups and accounts for more than 36% of all strokes in individuals aged 80 years and over [38]. Thus, stroke prevention is central to the management of patients with AF. Treatment decisions involving antithrombotic therapy should be made based on stroke risk assessment results by using the contemporary risk stratification method: CHA_2DS_2-VASc (1 point assigned for Congestive heart failure (CHF), Hypertension (HTN), Diabetes mellitus (DM), Vascular disease, Age 65-74 years, female gender and 2 points for age ≥ 75 years and prior stroke/TIA or thromboembolism) or the previous scoring method $CHADS_2$ (1 point each for CHF, HTN, Age ≥ 75 years, DM and 2 points for prior stroke or TIA [124,125]. The majority of patients with AF in clinical practice are at high risk of stroke (CHA_2DS_2-VASc ≥2) and high proportions of patients are in need of thromboprophylaxis [95].

Current AF treatment guidelines recommend oral anticoagulants (OACs) over APT agents in patients with moderate to high risk of stroke [18,76]. Despite controversy regarding its efficacy and safety, some guidelines continue to suggest low-dose aspirin in patients with low to moderate risk of stroke (CHA_2DS_2-VASc score = 0–1) as an alternative to OAC therapy [10,177]. Observational studies have typically demonstrated under-use of anticoagulants in patients who are eligible to receive them, and that APT agents are commonly used among patients with AF including those at higher risk of stroke ($CHADS_2$ or CHA_2DS_2-VASc ≥ 2) [138,266,267].

Since the 1950s, vitamin K antagonists (VKAs) were the only available OACs and most widely used antithrombotic agents for stroke prophylaxis in patients with AF [81,83]. In recent years, four direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban and edoxaban, have been approved for the prevention of stroke associated with non-valvular AF (NVAF). The introduction of the DOACs has resulted in significant changes in the therapeutic landscape of stroke prevention in AF and other cardio-embolic diseases [268,269]. Studies regarding recent antithrombotic prescribing practices in general and the integration of DOACs into clinical practice, in particular, are emerging from different countries [242,270]. These studies have shown some improvement in OAC prescribing, with DOACs increasingly being prescribed in preference to warfarin. However, a considerable percentage of high-risk patients continue to be treated with APT agents or remain untreated.

DOACs were approved for use in Australians with NVAF by the Australian Therapeutic Goods Administration (TGA) in 2011 [271], but their listing on the Australian Pharmaceutical Benefits Scheme (PBS) for subsidy by the Government was more recent; rivaroxaban was Government subsidised in August 2013, while apixaban and dabigatran were listed on the PBS in September 2013 [272]. The Tasmanian AF (TAF) study was established in 2012 with the aim of observing the use of anticoagulants, and the outcomes of treatment with anticoagulants, in Tasmanian patients with AF. The aim of this analysis was to investigate the utilisation patterns of antithrombotic therapies for stroke prevention in AF between 2011 and 2015, and observe changes in anticoagulant prescribing prior to, during, and following the introduction of DOACs in Australia.

3.3 Methods

3.3.1 Study design

We conducted a hospital-based, retrospective cohort study of patients aged ≥ 18 years admitted to the Royal Hobart Hospital (RHH) with a primary or secondary diagnosis of AF. The RHH is the largest referral hospital in the state of Tasmania, Australia, and provides clinical services for a population of approximately 240,000 people in Southern Tasmania. Electronic medical records of all patients with AF admitted from January 2011 to July 2015 were used as the data source. Patients' electronic medical record contained information including date of birth, gender, primary and secondary diagnosis, associated comorbidities, medication history, and laboratory data. Patients were identified by the Medical Record Department using Australian Refined Diagnosis Related Groups (AR-DRG) codes. AR-DRG code I48 was used for screening atrial fibrillation or flutter. Study subjects were excluded if they: (i) developed AF due to a complication of an acute illness, (ii) were diagnosed with AF due to a coding error, or (iii) had a single episode of AF that reverted spontaneously upon cardioversion without any documented recurrence. Because our aim was to assess antithrombotic prescribing patterns in the study population (as opposed to a focus only on DOACs), we included patients with valvular and non-valvular AF.

Patient demographics (gender, admission and discharge dates, alcohol use including estimated amount per week, smoking status), primary and secondary admission diagnosis, medical history, admission and discharge medications and laboratory data were entered in an online study database. The Charlson Comorbidity Index (CCI),[273] CHA_2DS_2-VASc,[125] and $CHADS_2$ [124] were calculated based on patient-specific comorbidities. The HAS-BLED score

(1 point each for HTN, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalised Ratio, (INR, as documented in the medical record), Elderly age ≥ 65 years, Drugs (APT agents or non-steroidal anti-inflammatory drugs or alcohol use > 8 units/week) [127] was also calculated. All antithrombotic therapies prescribed at hospital discharge were recorded.

To enable review of temporal trends in antithrombotic prescribing, antithrombotic users were defined as patients prescribed OACs (warfarin, apixaban, rivaroxaban, dabigatran) or APT medications. We categorised antithrombotic users into three cohorts based on the antithrombotic medication prescribed at discharge of their index admission (episode-1 during the study period): i) warfarin - patients with AF discharged on lone warfarin or warfarin-APT combination therapy, ii) DOAC - patients with AF discharged on lone dabigatran, rivaroxaban or apixaban, or DOAC-APT combination therapy, iii) APT agents - patients with AF prescribed lone APT or combination APT therapy. Temporal trends of antithrombotic prescribing were assessed by organising the admissions into quarterly (Q) periods. The proportions of patients prescribed warfarin, DOACs or APT agents (in the absence of an OAC) in each quarter were determined by dividing the number of patients prescribed each agent by total patients prescribed an antithrombotic within the respective period.

Persistence to antithrombotic therapy (antithrombotic survival analysis) was limited to patients admitted after PBS listing of DOACs (August 1, 2013). The analysis was conducted by following each patient discharged with the respective antithrombotic until a switch to another antithrombotic or cessation due to adverse effects or an emergence of a contraindication(s) (CI(s)). CIs to antithrombotic therapy were defined as documented evidence of recent bleeding while on antithrombotic therapy, severe anaemia, bleeding diathesis, clotting factor

deficiencies, dementia, and psychosis; additional contraindications for specific agents or classes included valvular AF for all DOACs, renal impairment (GFR< 30 mL/min for dabigatran, GFR<15 mL/min for rivaroxaban and apixaban), and pregnancy for all OACs. Subjects were censored at death or end of the study period (July 30, 2015). For each cohort, a Kaplan-Meier drug-survival plot was produced for the proportion of patients still being treated during follow-up. Comparison of patient characteristics among cohorts was limited to patients newly diagnosed with AF and initiated on antithrombotic therapy.

3.3.2 Statistical analysis

Continuous variables were described using mean $\pm$ standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were reported as frequency counts and percentages. Temporal trends in antithrombotic prescribing patterns per quarter were calculated as proportions and presented graphically. Quarterly proportions, including the linearity for increasing or decreasing trend, were tested based on the null hypothesis of no trend in the utilisation patterns for each antithrombotic therapy. Antithrombotic survival analyses were based on the time to the first event (drug discontinuation or change to an alternative agent), and a Kaplan-Meier antithrombotic-survival plot was produced for each cohort of antithrombotic users. Comparisons of patient characteristics were performed using the independent sample *Student's t-test* or *Mann-Whitney U-test* for continuous variables and the *chi-square test* for categorical variables. Data was analysed using R, version 3.2.3 (R Foundation for statistical computing, Vienna, Austria). A p-value of < 0.05 was considered statistically significant for all analyses.

3.4 Results

A total of 3265 patient records were reviewed. Of these, 2390 (73.2%) fulfilled our inclusion criteria and 875 (26.8%) were excluded. Three hundred and sixteen patients were excluded because AF was due to a complication of an acute illness, 341 because they had one episode of AF that reverted spontaneously upon cardioversion and without documented recurrence, and 218 because they were diagnosed to have AF due to a coding error. Eighty patients died during their index admission, leaving 2310 patients available for follow-up.

3.4.1 Study population characteristics

Patient demographics, comorbidities, and baseline stroke and bleeding risk scores are summarised in Table 6. The mean age of the study subjects was 74.8 years (standard deviation [SD] = 11.5), 44.6% were females, and hypertension was the most frequent comorbidity (61.5%). Mean (SD) $CHADS_2$ and CHA_2DS_2-VASc scores were 1.7 (1.1) and 3.2 (1.5), respectively. Only 96 (4.2%) patients were at low predicted risk of stroke (CHA_2DS_2-VASc = 0), while most (85.7%) patients were at high risk of stroke (CHA_2DS_2-VASc $\geq$ 2) during the index admission. Seven hundred and thirty-four (31.8%) patients had high bleeding risk scores (HAS-BLED $\geq$ 3).

3.4.2 Antithrombotic prescribing

Antithrombotic prescribing at the discharge of their index admission (episode-1) for our study population is summarised in Table 6. Of the 2261 (97.9%) study participants without a documented CI to any available antithrombotic therapy, 2078 (91.9%) were prescribed antithrombotic agents. One thousand three hundred and three (57.6%) patients received lone

OAC or OAC-APT combination therapy; 920 (40.7%) received warfarin alone or combined with APT therapy and 383 (16.9%) were prescribed DOACs (lone or combined with APT agents). APT therapy was prescribed for 745 (33.0%) and heparins or derivatives were prescribed for 30 (1.3%) patients. Forty-nine patients had a documented CI to all available antithrombotic therapies. The majority of these patients had their antithrombotic ceased prior to discharge due to an adverse drug reaction (ADR) related to their antithrombotic therapy.

Table 6. Baseline characteristics of patients with atrial fibrillation (January 2011 to July 2015).

Characteristics		**All patients (n = 2310)**
Age , mean (SD)		74.8 ± 11.5
Sex, (F), n (%)		1029 (44.6)
Alcohol use (>8 units /week), n (%)		159 (6.9)
Hospital stay in days, median (IQR)		5 (8)
CCI, mean (SD)		4.4 (2.2)
Comorbidities, n (%)	Hypertension	1420 (61.5)
	Ischaemic heart diseases	701 (30.3)
	Diabetes mellitus	500 (21.6)
	Chronic respiratory disease	477 (20.6)
	Congestive heart failure	429 (18.6)
	Myocardial infarction	249 (10.8)
	Valvular heart disease	216 (9.4)
	Renal disease	213 (9.2)
	History of stroke	156 (6.7)
	Peptic ulcer disease	119 (5.1)
	Other embolic events [a]	109 (4.7)
	Cerebrovascular disease	85 (3.7)

Characteristics		All patients (n = 2310)
	Prior bleeding	45 (1.9)
AF history, n (%)	First detected	812 (35.2)
	Pre-existing	1498 (64.8)
CHA_2DS_2-VASc	Mean, (SD)	3.2 (1.5)
	CHA_2DS_2-VASc = 0, n (%)	96 (4.2)
	CHA_2DS_2-VASc =1, n (%)	234 (10.1)
	CHA_2DS_2-VASc $\geq$ 2, n (%)	1980 (85.7)
$CHADS_2$	Mean, (SD)	1.7 (1.1)
	$CHADS_2$ = 0, n (%)	329 (14.2)
	$CHADS_2$ = 1, n (%)	676 (29.3)
	$CHADS_2$ $\geq$ 2, n (%)	1305 (56.5)
HAS-BLED score	Median (IQR)	2 (1)
	HAS-BLED $\geq$ 3, n (%)	734 (31.8)
Patients with documented CI to antithrombotic, n (%)		49 (2.1)
Patients without CI to antithrombotic therapy, n (%)		2261 (97.9)
Overall antithrombotic prescribing	Antithrombotic prescribed at discharge, n (%)*	2078 (91.9)
	No therapy, n (%)	183 (8.1)

Characteristics		All patients (n = 2310)
Antithrombotic group prescribed at discharge, n (%)	Warfarin (lone and with APT)	920 (40.7)
	DOAC (lone and with APT)	383 (16.9)
	APT (lone and combination)	745 (33.0)
	Heparin or derivatives	30 (1.3)

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulant; APT, antiplatelet agent; CCI, Charlson comorbidity index; SD, standard deviation; IQR, interquartile range; CI, contraindication. [a] Other embolic events include patients with history of deep venous thrombosis and pulmonary embolism. *The percentages of patients receiving various antithrombotic medications at discharge were calculated using the number of patients without a documented contraindication to antithrombotic therapy (n=2261).

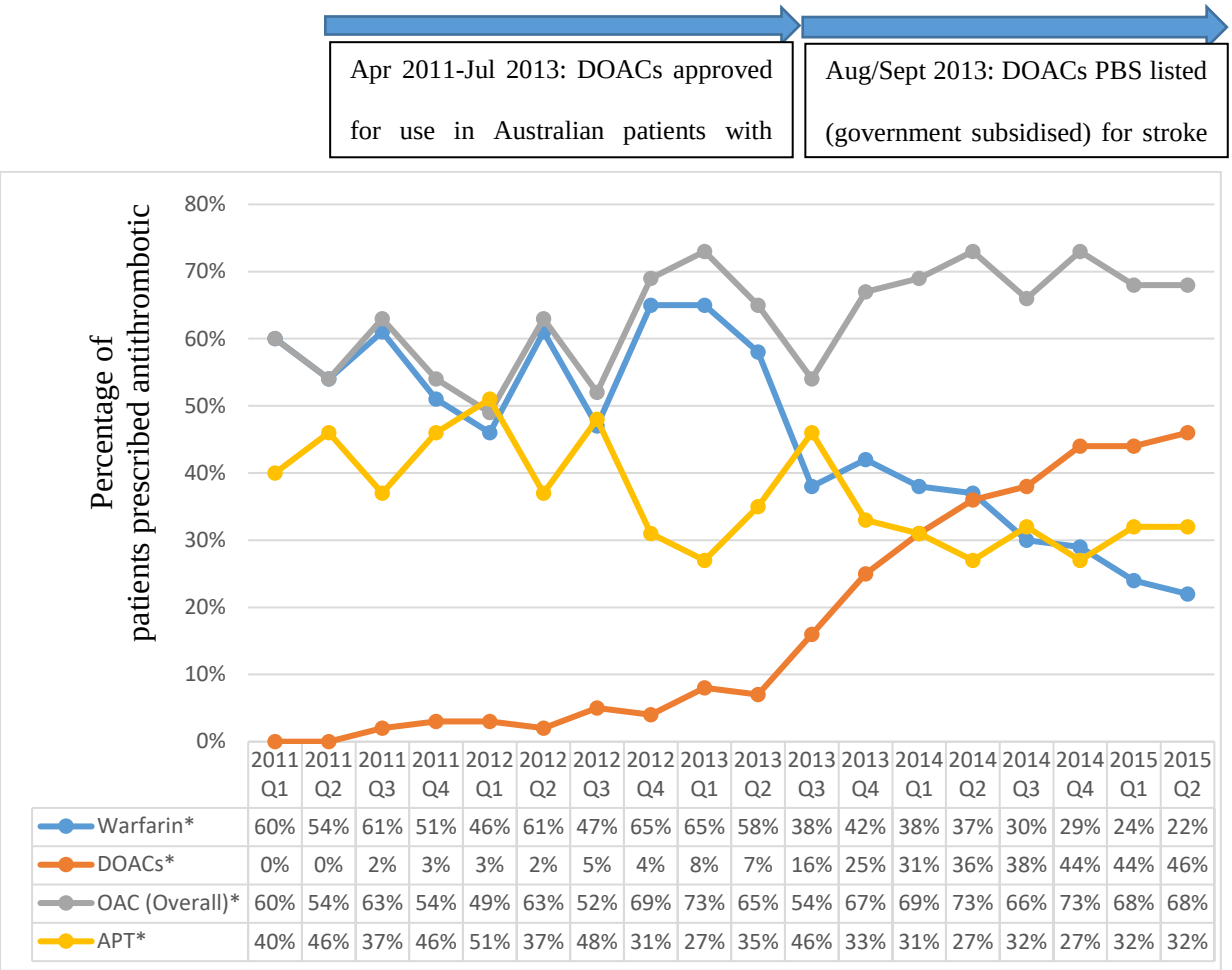
3.4.3 Temporal antithrombotic utilisation patterns

The temporal utilisation patterns of OACs and APT agents are illustrated in Figure 7. The utilisation of warfarin and individual DOACs are presented in Figure 8. A consistently higher proportion of patients were prescribed OACs during the later quarters (Q), (Q4, 2013 to Q2, 2015), largely explained by the introduction of DOACs. In earlier Qs of our study (Q1, 2011 to Q2, 2014), warfarin was the most commonly prescribed antithrombotic.

DOACs were available for patients with NVAF from Q3, 2011, although they did not become Government-subsidised until mid-late 2013. Prescribing of DOACs among patients discharged on OAC therapy steadily increased from 3.9% in Q3, 2011 to 67.6% in Q2, 2015 ($p < 0.001$). Uptake of the DOACs was rapid following the availability of Government subsidisation and, as a class, they became the most commonly prescribed agents from Q3, 2014 to the end of our

study period. In contrast, the prescribing of warfarin significantly declined from Q3, 2013 to Q2, 2015 (38.1% vs. 22.1%, $p < 0.001$). Further, a significant decline in the prescribing of APT agents alone (in the absence of an OAC) was observed when proportions across all quarters were compared (39.8% in Q1, 2011 to 31.9% in Q2, 2015, $p < 0.001$).

Analysis of the utilisation patterns of individual OACs showed that warfarin prescribing dropped steadily ($p <0.001$ for decreasing trend) while dabigatran prescribing remained stable at low proportions ($p = 0.07$) over the follow-up period. Rivaroxaban and apixaban prescribing increased rapidly, mainly later in the study period. A rapid decline in warfarin prescribing was noticeable from Q2, 2013 to Q2, 2015 (94.2% to 32.4%, $p < 0.001$), with a corresponding increase in the uptake of DOACs in the same period (5.8% to 67.6%, $p < 0.001$). In the final quarter of the study period (Q2, 2015), apixaban was the most commonly prescribed OAC (33.8%), followed by warfarin (32.4%) and rivaroxaban (24.7%) while dabigatran was prescribed for 9.1% of the OAC users.

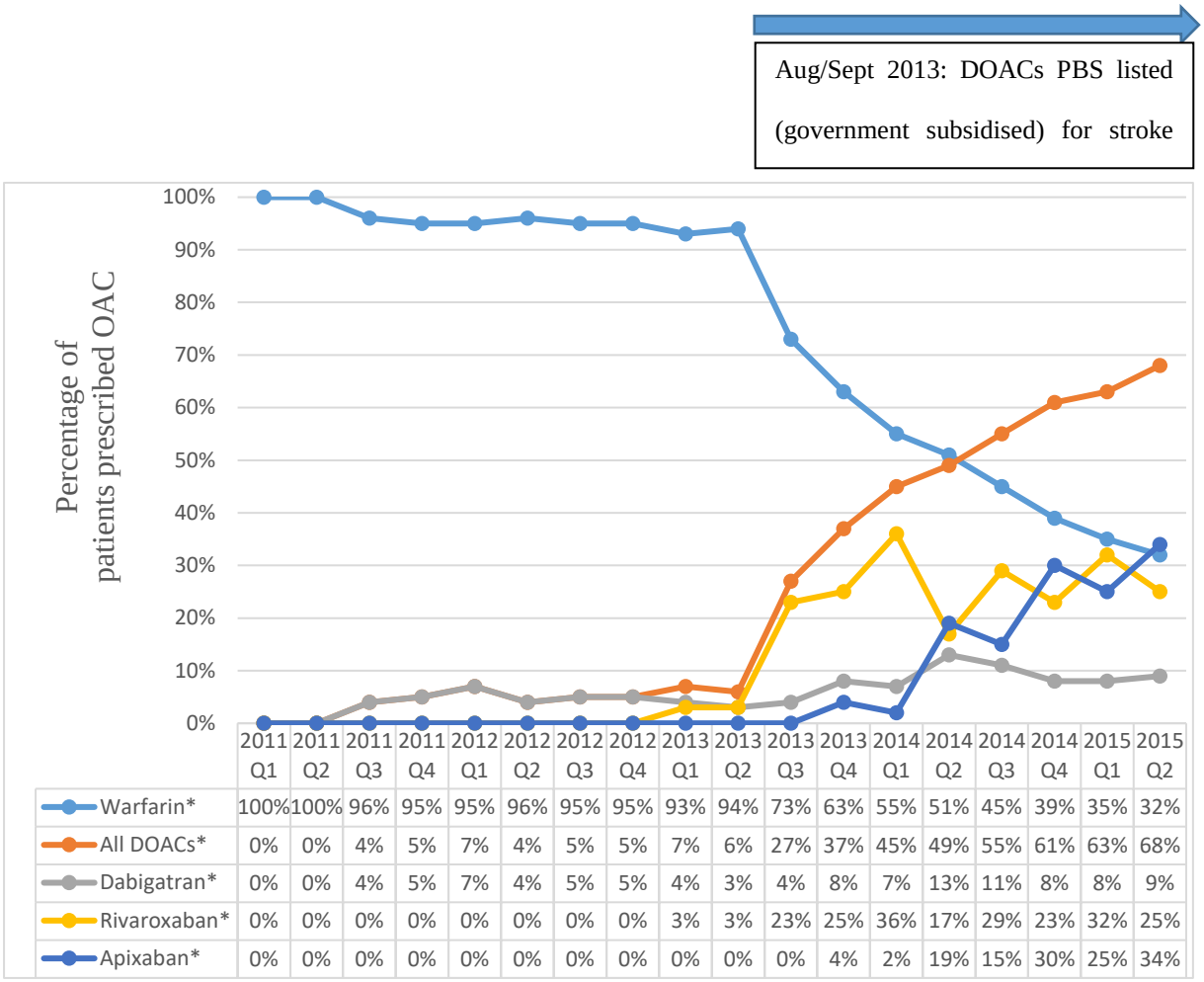


	2011 Q1	2011 Q2	2011 Q3	2011 Q4	2012 Q1	2012 Q2	2012 Q3	2012 Q4	2013 Q1	2013 Q2	2013 Q3	2013 Q4	2014 Q1	2014 Q2	2014 Q3	2014 Q4	2015 Q1	2015 Q2
Warfarin*	60%	54%	61%	51%	46%	61%	47%	65%	65%	58%	38%	42%	38%	37%	30%	29%	24%	22%
DOACs*	0%	0%	2%	3%	3%	2%	5%	4%	8%	7%	16%	25%	31%	36%	38%	44%	44%	46%
OAC (Overall)*	60%	54%	63%	54%	49%	63%	52%	69%	73%	65%	54%	67%	69%	73%	66%	73%	68%	68%
APT*	40%	46%	37%	46%	51%	37%	48%	31%	27%	35%	46%	33%	31%	27%	32%	27%	32%	32%

Figure 7. Temporal antithrombotic utilisation patterns, January 2011 to July 2015.

Abbreviations: NVAF, Non-valvular atrial fibrillation; OAC, oral anticoagulant; DOAC, direct oral anticoagulant; APT, antiplatelet agents; Q, quarter. *Groups consisted of lone agents or OAC-APT combination therapy. Percentages are rounded to the nearest integer.

Note: Each quarter (Q) includes all patients with AF discharged within that three-month period and prescribed antithrombotic therapy at discharge of their index admission. Q1 = January-March, Q2 = April-June, Q3 = July-September, Q4 = October-December. DOACs were approved by the Therapeutic Goods Administration (TGA) for use in the Australian patients with NVAF in April 2011, and subsequently listed on the Pharmaceutical Benefits Scheme (PBS) for government subsidy in August 2013.



	2011 Q1	2011 Q2	2011 Q3	2011 Q4	2012 Q1	2012 Q2	2012 Q3	2012 Q4	2013 Q1	2013 Q2	2013 Q3	2013 Q4	2014 Q1	2014 Q2	2014 Q3	2014 Q4	2015 Q1	2015 Q2
Warfarin*	100%	100%	96%	95%	95%	96%	95%	95%	93%	94%	73%	63%	55%	51%	45%	39%	35%	32%
All DOACs*	0%	0%	4%	5%	7%	4%	5%	5%	7%	6%	27%	37%	45%	49%	55%	61%	63%	68%
Dabigatran*	0%	0%	4%	5%	7%	4%	5%	5%	4%	3%	4%	8%	7%	13%	11%	8%	8%	9%
Rivaroxaban*	0%	0%	0%	0%	0%	0%	0%	0%	3%	3%	23%	25%	36%	17%	29%	23%	32%	25%
Apixaban*	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	4%	2%	19%	15%	30%	25%	34%

Figure 8. Temporal oral anticoagulant utilisation patterns, January 2011-July 2015.
Abbreviations: NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; DOAC, direct oral anticoagulant; Q, quarter. *Groups consisted of lone agents or combined OAC and antiplatelet agents. Percentages are rounded to the nearest integer.

3.4.4 Antithrombotic survival

A Kaplan-Meier plot of antithrombotic survival is presented in Figure 9. The plot shows the probability of drug survival at the given time intervals (months) and rates of switching to an alternative agent, drug discontinuation due to ADR, or emergence of a CI to antithrombotic therapy. We included 973 patients admitted after August 1, 2013 and prescribed antithrombotic

agents (warfarin = 309, DOACs = 360, and APT agents = 304) at discharge of their index admission. The mean (95% CI) survival time in months for the three groups were: 22.4 (20.3-22.0) for DOACs, 21.9 (21.2-23.1) for warfarin and 21.1 (20.3-22.0) for APT agents. The Log-rank, Breslow, and Tarone-Ware test of survival distribution showed a significant difference between the cohorts (p = 0.04, 0.009 and 0.016, respectively).

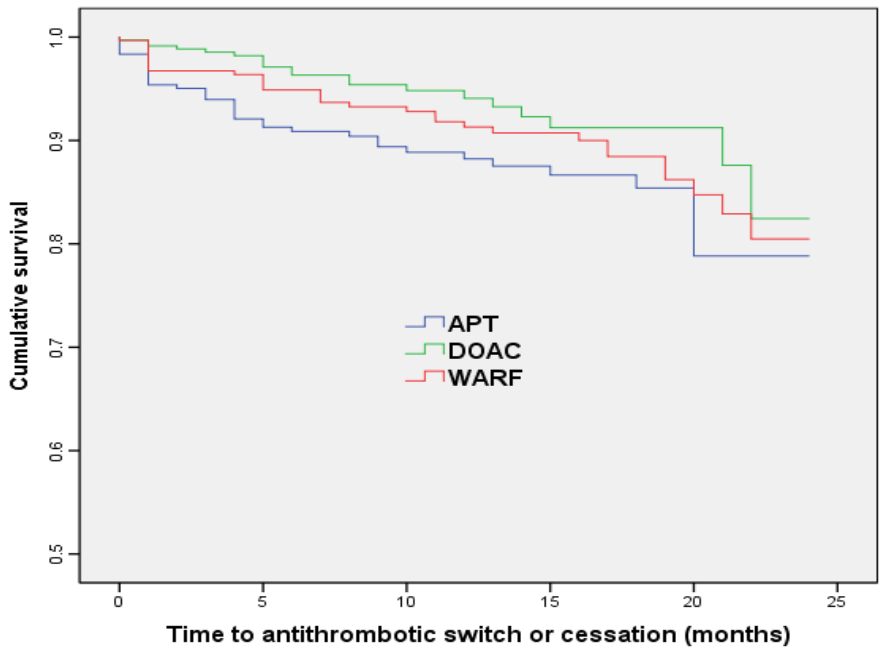


Figure 9. Kaplan-Meier plot of drug survival among antithrombotic users in atrial fibrillation. **Abbreviations**: APT, antiplatelet; DOAC, direct oral anticoagulant; WARF, warfarin.

3.4.5 Warfarin versus DOAC prescribing in newly diagnosed AF

We conducted a sub-analysis of 364 patients with newly diagnosed AF who were admitted to the RHH from August 1, 2013, to compare the characteristics of subjects prescribed APT agents, warfarin, and DOACs. Seven patients died during the index admission, three patients had a documented contraindication to antithrombotic therapy, and 51 were discharged without antithrombotic therapy. Antithrombotics were prescribed for 303 patients; warfarin was

prescribed for 56 patients, DOACs for 140 patients, and APT therapy (in the absence of an OAC) for 107 patients. Table 7 summarises the baseline characteristics of these cohort. Patients treated with DOACs were younger (mean age 70.4 vs. 73.8 years, $p = 0.04$) and had a lower comorbidity (mean CCI 3.5 vs. 4.7, $p < 0.001$) than patients treated with warfarin. Patients prescribed DOACs had a significantly lower predicted stroke risk (mean CHA_2DS_2-VASc 2.8 vs. 3.3, $p = 0.03$), and bleeding risk scores (median HAS-BLED 2 vs. 3, $p = 0.04$) compared to warfarin users. There were no significant differences in the characteristics of patients prescribed OACs compared to patients prescribed APT agents.

Table 7. Baseline characteristics of patients newly diagnosed with atrial fibrillation according to prescribed antithrombotic agents.

Variable	DOAC (n = 140) [a] vs. Warfarin (n = 56) [b]		p-value	OAC (n = 196) [c] vs. Antiplatelet (n = 107) [d]		p-value
Gender (F), n (%)	65 (46.4)	22 (39.3)	0.450	87 (44.4)	49 (45.8)	0.910
Age (years), Mean (SD)	70.4 (11.1)	73.8 (8.6)	0.040	71.3 (10.6)	73.8 (13.0)	0.080
$CHADS_2$, Mean (SD)	1.5 (1.1)	1.7 (1.2)	0.210	1.5 (1.2)	1.4 (1.1)	0.720
CHA_2DS_2-VASc, Mean (SD)	2.8 (1.5)	3.3 (1.4)	0.030	2.9 (1.4)	2.8 (1.5)	0.880
HAS-BLED score, Median (IQR)	2 (0.3)	3 (1)	0.040	2 (1)	2 (1)	0.080
Hospital stay, Median (IQR)	3 (6)	6 (9)	0.002	3 (8)	4 (10)	0.070
CCI, Mean (SD)	3.5 (2.3)	4.8 (2.0)	<0.001	3.8 (2.3)	3.9 (2.5)	0.960

Abbreviations: DOAC, direct oral anticoagulant; OAC; oral anticoagulant; CCI, Charlson comorbidity index; SD, standard deviation; IQR, interquartile range. [a] Included patients discharged with lone dabigatran, rivaroxaban, apixaban or these therapies combined with antiplatelet agents. [b] Included patients discharged with lone warfarin or warfarin-antiplatelet combination therapy. [c] Included patients discharged with warfarin, one of the DOACs alone or combined with antiplatelet therapy. [d] Included patients discharged with aspirin, clopidogrel or dipyridamole, either alone or in combination

3.5 Discussion

This study assessed contemporary utilisation patterns of antithrombotic therapy in patients admitted to the Royal Hobart Hospital in Tasmania, Australia with AF. It is among the first Australian studies to provide detailed information from a real-world clinical setting on antithrombotic prescribing patterns before, during and after the introduction of DOACs.

DOACs have clearly become the agents of choice for stroke prevention in NVAF. We observed a slight and steady increase in the number of patients receiving DOACs from Q3, 2011 to Q2, 2013. Uptake of the new agents, however, became rapid from Q3, 2013 onwards. Analysis of admissions from the later quarters of our study (Q3, 2014 onwards) showed that the majority of patients receiving an OAC were prescribed a DOAC, accounting for 54.7%, 60.8%, 64.7% and 67.5% of OAC prescribing during the last four quarters of the study period. Conversely, the proportion of patients discharged on warfarin declined rapidly in the same period. Moreover, a statistically significant reduction in APT prescribing was observed during the study period. This corresponded with the commencement of Government subsidy of the new agents. Nonetheless, APT agents accounted for a quarter to a third of all antithrombotic prescribing after Q3, 2013 to the end of our study period.

Overall, a consistently higher OAC prescribing was observed during the last seven quarters whereas there was a significant decline in warfarin prescribing in the same period. This suggested the growth in OAC prescribing was due to an increase in DOACs initiation. While this can be considered as an essential step towards addressing suboptimal OAC use in eligible patients with AF as observed in multiple observational studies [95,269], there remains a

significant proportion of patients at moderate-high risk of stroke receiving APT medications who may benefit from the prescribing of an anticoagulant medication.

In line with our results, a study on the uptake of the new agents using the administrative claims data from the Australian Government Veterans' Affairs (including all indications for OACs) showed an overall increase in OAC and a sharp increase in DOAC use; warfarin prescribing declined after the new agents were listed on PBS [274]. A small study from Manning Base Hospital, New South Wales, Australia, also observed rapid growth in the prescribing of DOACs; more patients were reported to have been anticoagulated for AF compared to earlier practices. However, warfarin prescribing remained stable and the increase in DOAC use was not attributed to a reduction in warfarin prescribing [275].

Over the study period, we observed that rivaroxaban was the most (49.2%) prescribed DOAC followed by apixaban (29.6%) and dabigatran (21.2%). A modest increase in dabigatran prescribing was observed in the later quarters of 2014, followed by a slight decline in the last two study quarters. Analogous to our finding, a study of patients receiving long-term anticoagulation in the USA reported rivaroxaban (55.3%) as the most prescribed DOAC followed by apixaban (22.5%) and dabigatran (22.2%) [276]. Other studies on trends of OAC use from European countries and Canada showed a growing share of DOACs among OAC prescriptions and decreasing trend of warfarin prescribing in recent years [277,278]. Increased prescribing of DOACs in eligible patients with AF was an anticipated phenomenon as the new agents offer comparable efficacy, better safety, and fewer interactions with drugs and food than warfarin [276]. In the last quarter of the study period, apixaban was the most commonly prescribed OAC.

In the antithrombotic survival analysis (Figure 9), patients discharged on DOACs had a higher persistence to treatment than warfarin or APT agents; and this was mainly explained by a higher rate of switch from warfarin or APT agents to DOACs. Moreover, further analysis on readmitted patients revealed a higher proportion of drug discontinuation due to ADRs and emergent contraindications among warfarin and APT users compared to DOAC users. This finding, however, should be interpreted with caution, as DOACs were prescribed for younger patients with less comorbidity, who may therefore be less likely to experience ADRs as a result.

Contrasting reports are emerging in regards to persistence to therapy among patients on OAC therapy. Analogous to our findings, a study measuring 6-, 9-, and 12-month persistence from the United States Department of Defence administrative claims data showed significantly higher rates of persistence among dabigatran compared to warfarin users. A similar study on 27,514 OAC-naïve patients from primary care Clinical Practice Research Datalink in the United Kingdom indicated persistence with OACs declined within 12 months to 63.6% for VKAs and 79.2% for DOACs ($p<0.001$) [279,280]. In contrast, observational studies from Japan and Denmark reported lower persistence rates among DOAC compared to warfarin users with a large proportion of DOAC users switched to a VKA within six months of follow-up [281,282]. The reasons for early discontinuation of DOACs in the Japanese patients were ADRs, worsening renal dysfunction, and patient choice; while the reason for early switching in the Denmark study was not explained.

Comparative analysis of patients with newly diagnosed AF who were initiated on OACs showed that DOACs were prescribed to younger patients with fewer comorbidities than their warfarin counterparts. Moreover, the DOACs were prescribed to patients with lower predicted risk of stroke and bleeding than those prescribed warfarin. This might reflect a more

conservative approach to prescribing the new agents among elderly patients with more comorbid conditions, or in patients with diminished renal function.

Similar to our findings, a registry study in the ORBIT-AF reported patients receiving dabigatran were younger and had lower stroke and bleeding risk scores than patients who did not receive dabigatran [230]. Another study on factors driving OAC selection in patients with AF in the USA also showed higher bleeding and stroke risk scores associated with warfarin initiation compared to DOAC initiation [246]. Randomised controlled trials established that DOACs had comparable efficacy in preventing stroke and systemic embolism, but were significantly safer than warfarin, primarily when ICH was considered [99,105,276]. It follows that initiating DOACs in elderly patients with more comorbid conditions may lead to improved clinical outcomes.

3.6 Conclusion

DOACs rapidly became the most commonly prescribed class of antithrombotic medications in patients with AF soon after they became widely available. Warfarin and APT prescribing declined significantly, although a substantial proportion of patients continued to be prescribed APT therapy in preference to an anticoagulant. Patients who were initiated on DOACs were typically younger with fewer comorbid conditions compared to those initiated on warfarin therapy. Patients who were prescribed DOACs tended to persist on therapy longer than patients prescribed warfarin or APT agents.

CHAPTER FOUR

4. Changes in oral anticoagulant prescribing for stroke prevention in patients with atrial fibrillation.

Overview

This study was undertaken to address the second objective of the thesis, i.e. to evaluate the impact of the availability of DOACs on OAC prescribing practices in patients with NVAF. We hypothesised that there would be a net increase in OAC prescribing over time, driven primarily by a greater use of DOACs. In this analysis, we compared anticoagulation practices before and after DOACs became widely available in Australia, and investigated OAC prescribing by stroke risk stratification, using current AF guidelines. We also identified factors independently associated with OAC prescribing in AF. This paper was published in the American Journal of Cardiology (https://www.ncbi.nlm.nih.gov/pubmed/28781025) on October 1, 2017.

4.1 Abstract

Suboptimal guideline adherence and underuse of anticoagulants in patients with atrial fibrillation (AF) have been reported worldwide. This study aimed to compare anticoagulation practice in Australia during the pre- and post-direct oral anticoagulant (DOAC) eras. Between January 2011 and July 2015, patients with non-valvular AF (NVAF) admitted to the Royal Hobart Hospital, Tasmania, Australia, were retrospectively reviewed. The pre- and post-DOAC era cohorts included admissions from January 2011 to July 2013 and August 2013 to July 2015, respectively. Anticoagulation practices were compared in the two eras using contemporary guideline recommendations for oral anticoagulant (OAC) use in AF. Overall, 2118 patients (1089 from the pre-DOAC and 1029 from the post-DOAC era) met our inclusion criteria. The overall rate of anticoagulation increased from 52.5% in the pre-DOAC era to 60.7% in the post-DOAC era ($p < 0.001$). Moreover, prescribing of OACs among high-risk patients improved significantly (63.1% vs 55.2%, $p = 0.001$). OAC over-prescribing in low-risk patients did not change significantly between the two cohorts (35.0% vs 42.9% in the pre- and post-DOAC eras, respectively, $p = 0.59$). In multivariate analysis, DOAC era (odds ratio [OR], 1.40, 95% CI 1.17–1.68) and CHA_2DS_2-VASc $\geq$ 2 (OR 1.95, 95% CI 1.36–2.80) were independent predictors of OAC prescribing in both eras and the whole study period. Conversely, aging and prior bleeding were inversely associated with OAC prescribing. In conclusion, there has been a significant increase in OAC prescribing in the post-DOAC era, potentially driven by the widespread availability of DOACs. However, OAC underuse in high-risk and overuse in low-risk patients was apparent throughout our study. These findings highlight the need to identify the drivers of anticoagulant under- and over-use and address them accordingly.

Keywords: atrial fibrillation; stroke; oral anticoagulant; warfarin; direct oral anticoagulant.

4.2 Introduction

Effective utilisation of oral OACs is essential in the management of patients with atrial fibrillation (AF) [283]. For many decades, vitamin K antagonists (VKAs) were the most effective treatment in AF, reducing stroke and systemic embolism by 60% to 70% compared to placebo [86,111]. However, suboptimal use of VKAs, such as under-prescribing in high stroke risk, and over-prescribing in low-risk patients, was frequently reported in observational studies [95,269]. Since 2010, four direct-acting oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, have been approved for stroke prevention in patients with non-valvular AF (NVAF). Post-marketing AF-registry studies and local data from clinical settings show significant uptake of DOACs for stroke prevention in NVAF [284-286]. Nonetheless, data is conflicting as to whether DOACs are being used as therapeutic substitutes for VKAs, or there is an overall increase in OAC prescribing following the approval of the new agents [287]. The focus of the present analysis was to examine anticoagulation practices before and after DOACs became widely available in Australia, and to investigate whether DOAC availability was an independent predictor of OAC prescribing in NVAF.

4.3 Methods

Between January 2011 and July 2015, patients with NVAF admitted to the Royal Hobart Hospital (RHH), Tasmania, Australia, were assessed retrospectively using digital medical records as a data source. The Tasmanian Health and Medical Research Ethics Committee approved this study. Patients were identified using the Australian Refined Diagnosis Related Groups (AR-DRG) code I48 to screen for atrial fibrillation or flutter. Based on the definitions in current AF guidelines [9,10], patients with valvular AF (i.e. those with a documented history

of mitral stenosis and artificial heart valves) were excluded. However, we included patients with AF and other types of valvular heart disease (VHD) including mitral regurgitation, aortic regurgitation, aortic stenosis and mitral valve prolapse.

Demographic data including sex, age, smoking status and alcohol use as listed in the medical record were entered into an online study database. Further, admission diagnoses, comorbidities, admission and discharge medications, and laboratory data were reviewed and entered into the database. For the assessment of stroke or bleeding risk, CHA_2DS_2-VASc [125] and HAS-BLED [127] scoring methods were used respectively. Eligibility and OAC prescribing practices were assessed based on contemporary AF treatment guideline recommendations. For this purpose, we used European Society of Cardiology and the joint American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) AF guidelines [10,76]. Each patient's stroke risk score was calculated and categorised into three groups with anticoagulation recommendations as follows: i) low stroke risk (CHA_2DS_2-VASc = 0) - no antithrombotic therapy recommended, ii) intermediate stroke risk (CHA_2DS_2-VASc = 1) - guideline recommendations differ in this group; whereas the AHA/ACC/HRS guidelines recommend aspirin, OAC or no therapy, European guidelines recommend OAC for men, iii) high stroke risk (CHA2DS2-VASc $\geq$ 2) – all guidelines recommend OAC in this group.

To compare anticoagulation practices before and after government subsidy of DOACs, we grouped the study population into two cohorts based on index admission dates: i) pre-DOAC era (January 2011 to July 2013), and ii) post-DOAC era (August 2013 to July 2015). Rivaroxaban was first listed on the Pharmaceutical Benefits Scheme (PBS) for subsidy by the Australian Government, on 1 August 2013, followed by dabigatran and apixaban in September 2013 [272]. Thus pre-DOAC era, in this study, was defined as the time period at which DOACs

were at the early stages of clinical familiarisation in the Australian settings (between early 2011 and mid-2013). Post-DOAC era was defined as the time period after the new therapies were listed on the PBS until the end of our study period (mid-2013 to mid-2015).

Patients were considered anticoagulated if warfarin, dabigatran, rivaroxaban or apixaban was prescribed at discharge of their first (index) admission unless contraindicated (edoxaban has yet to be approved in Australia). Contraindications to OAC therapy included the following: recent bleeding while on an antithrombotic therapy, severe anaemia, bleeding disorders (bleeding diathesis, clotting factor deficiencies), dementia, psychosis, and pregnancy or breastfeeding. Patients without documented contraindication and discharged without any antithrombotic therapy were categorised as "no therapy". In patients not receiving an OAC, we reviewed the medical records for documented reasons for not prescribing an OAC.

Continuous variables were expressed as means and standard deviations (SD) and categorical variables as frequencies and percentages. Independent-sample *Student's t-tests* were used to compare continuous variables in two groups, and *Chi-square* and *Fisher's exact tests* were used for comparing categorical variables. Multivariate logistic regression modelling was used to identify factors associated with OAC prescribing in the pre-DOAC, post-DOAC, and overall study period. The threshold for entry into the multivariate model was set at $p \leq 0.25$. Multi-collinearity among predictor variables was checked using the variance inflation factor (VIF); $VIF \leq 3$ was taken for stable estimation of regression coefficients. All statistical analyses were conducted using R, version 3.2.5. A p-value < 0.05 was considered statistically significant.

4.4 Results

4.4.1 Baseline characteristics comparison

A total of 2,118 patients with NVAF, 1,089 from the pre-DOAC, and 1,029 from the post-DOAC eras, were included for assessment. Baseline patient characteristics are shown in Table 8. There were no statistically significant differences in the mean age, sex, stroke and bleeding risk scores, and most comorbidities between the two cohorts. According to contemporary risk score stratification methods and AF treatment guideline recommendations, most of our study subjects had high stroke risk scores at index admission and were in need of OAC therapy.

Table 8. Comparison of baseline characteristics of the study population

Variables	Pre-DOAC (n = 1089)	Post-DOAC (n =1029)	p-value
Age (years), mean (±SD)	74.7 ±11.6	74.9 ±11.6	0.605
Women	471(43.2%)	476 (46.3%)	0.178
Hospital stay (days), mean (±SD)	9.8 ±14.5	8.1 ±13.1	0.005
CCI, mean (±SD)	4.5 ± 2.2	4.3 ± 2.2	0.109
Hypertension	715 (65.6%)	607 (59.0%)	0.002
Ischaemic heart disease	365 (33.5%)	273 (26.5%)	< 0.001
Chronic respiratory disease	249 (22.9%)	189 (18.4%)	0.012
Diabetes mellitus	230 (21.1%)	229 (22.2%)	0.561
Congestive heart failure	181 (16.6%)	203 (19.7%)	0.072
Myocardial infarction	125 (11.5%)	101 (9.8%)	0.243
Renal disease	89 (8.2%)	112 (10.9%)	0.040
Past or current stroke	54 (4.9%)	96 (9.3%)	< 0.001
Other embolic events *	51 (4.7%)	50 (4.9%)	0.930
Valvular heart disease ¥	50 (4.6%)	51 (4.9%)	0.770
Peripheral vascular disease	44 (4.0%)	33 (3.2%)	0.911
Cerebrovascular disease	44 (4.0%)	35 (3.4%)	0.509
Prior bleeding history	25 (2.3%)	12 (1.2%)	0.069
Alcohol use (> 8 units /week)	83 (7.6%)	63 (6.1%)	0.202
CHA_2DS_2-VASc score, mean (±SD)	3.2 ±1.6	3.3 ±1.1	0.635
CHA_2DS_2-VASc = 0	43 (3.9%)	49 (4.8%)	

Variables	Pre-DOAC	Post-DOAC	p-value
CHA_2DS_2-VASc =1	116 (10.6%)	92 (8.9%)	
CHA_2DS_2-VASc ≥ 2	930 (85.4%)	888 (86.3%)	
HAS-BLED score, mean (±SD)	2.3 ± 0.77	2.2 ± 0.72	0.075
HAS-BLED = 0-1	112 (10.3%)	142 (13.8%)	
HAS-BLED = 2	625 (57.4%)	579 (56.3%)	
HAS-BLED ≥ 3	352 (32.3%)	308 (29.9%)	

Abbreviations: CCI, Charlson comorbidity index; DOAC, direct oral anticoagulant; SD, standard deviation. * Include patients with history of deep venous thrombosis and pulmonary embolism. ¥ Include patients with a history of mitral or aortic regurgitation, aortic stenosis, and mitral valve prolapse.

4.4.2 Antithrombotic prescribing at discharge

Overall prescribing of any antithrombotic (OAC or APT therapy) was significantly higher in the pre-DOAC era compared to the post-DOAC era (93.1% vs. 90.0%, p = 0.012). There was an absolute increase in the overall anticoagulant prescribing over time, from 52.5% in the pre-DOAC to 60.7% in the post-DOAC era (relative increase of 15.6%, p < 0.001) (Table 9). Prescribing of lone warfarin, lone APT agent, warfarin-APT, and combination APT therapy (without OAC) was higher in the pre-DOAC cohort.

When anticoagulation was analysed by the CHA_2DS_2-VASc score strata, OAC prescribing increased with increased stroke risk score in the two study populations (Figure 10). Comparing anticoagulation practices by stroke risk groups between the two eras, OAC prescribing was higher across all stroke risk groups in the post-DOAC era than OAC prescribing in the pre-DOAC era. OAC prescribing in high-risk patients improved in the post-DOAC era compared

to the pre-DOAC era (an absolute increase from 55.2% to 63.1%, relative increase of 14.3%, p = 0.001). There was no statistically significant change in OAC over-prescribing in the low-risk patients between the two periods. APT prescribing declined in the post-DOAC era across all stroke risk strata compared to the pre-DOAC era. However, a substantial proportion of high-risk patients were treated using APT therapy in both eras-38.9% in the pre-DOAC and 28.2% in the post-DOAC eras.

Table 9. Antithrombotic prescribing in the pre- and post-direct oral anticoagulant eras.

Prescribing at discharge, n (%)	Pre-DOAC (n =1089)	Post-DOAC (n= 1029)	p-value
All OACs [a]	572 (52.5%)	625 (60.7%)	< 0.001
All DOACs [b]	22 (2.0%)	348 (33.8%)	< 0.001
All APT agents [c]	421 (37.5%)	295 (28.7%)	< 0.001
Warfarin	380 (38.7%)	206 (20.0%)	< 0.001
Dabigatran	15 (1.4%)	52 (5.1%)	< 0.001
Rivaroxaban	4 (0.4%)	139 (13.5%)	< 0.001
Apixaban	0 (0.0%)	85 (8.3%)	< 0.001
Aspirin	336 (30.8%)	249 (24.2%)	< 0.001
Clopidogrel	33 (3.0%)	16 (1.5%)	0.035
Warfarin-APT combination	170 (15.6%)	71 (6.9%)	< 0.001
DOAC-APT combination	3 (0.3%)	72 (7.0%)	< 0.001
OAC-APT combination [d]	173 (16.9%)	143 (13.9%)	0.221
APT combination [e]	52 (4.8%)	30 (2.9%)	0.035
Heparin and derivatives	21 (1.9%)	6 (0.6%)	0.010
No therapy	75 (6.9%)	103 (10.0%)	0.012

Abbreviations: APT, antiplatelet; DOAC, direct oral anticoagulant; OAC, oral anticoagulant. [a] Includes all OACs (warfarin and DOACs) with or without antiplatelet therapy. [b] Includes lone apixaban, dabigatran, rivaroxaban, and DOAC-antiplatelet combination therapy. [c] Includes lone or dual-APT combination therapy. [d] Includes warfarin or a DOAC with antiplatelet combination therapy. [e] Includes APT combination without OAC therapy.

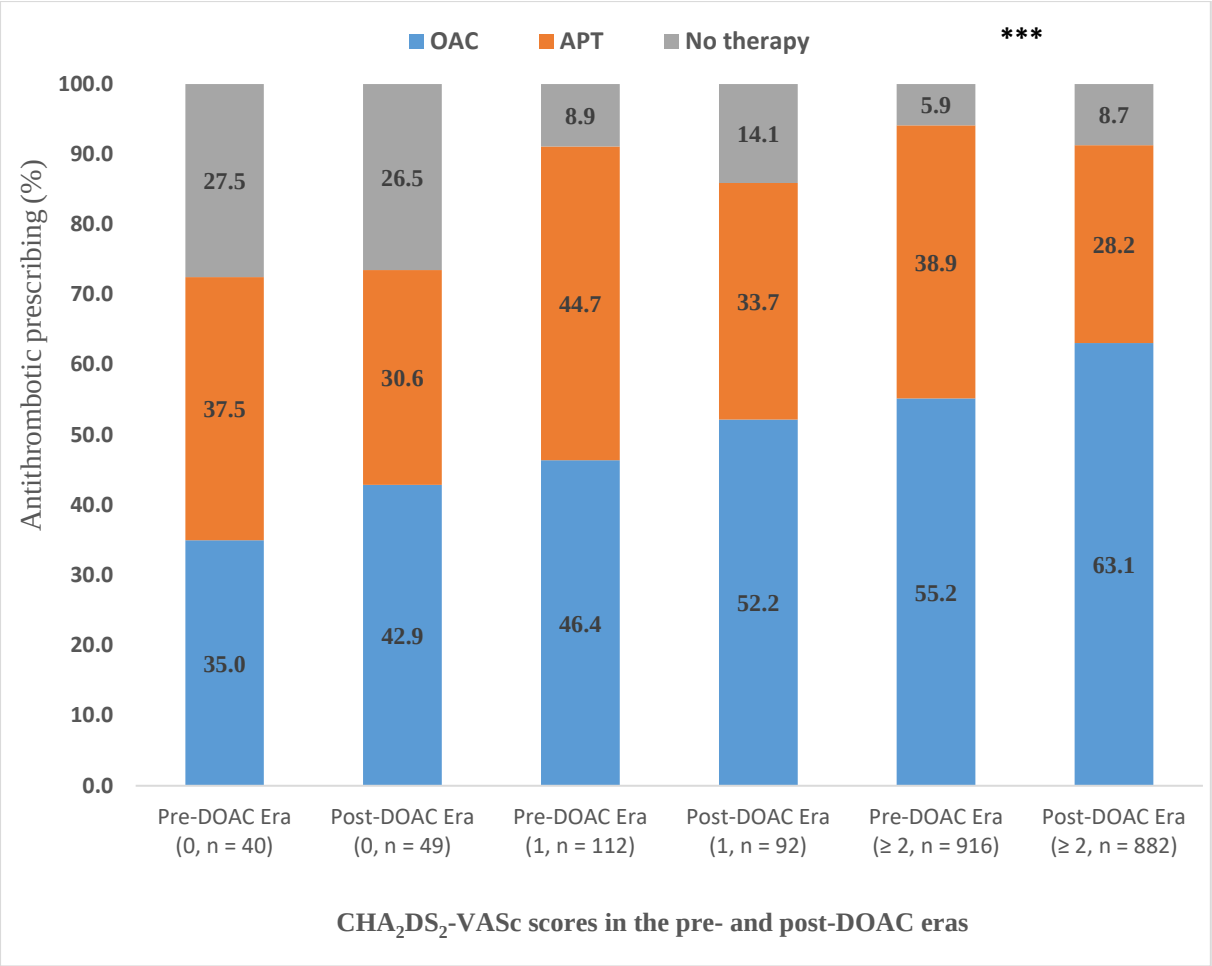


Figure 10. Antithrombotic prescribing stratified by stroke risk scores in the pre- and post-direct oral anticoagulant era.

*** P ≤ 0.001. Abbreviations: OAC, oral anticoagulant (with or without antiplatelet therapy); APT, antiplatelet (lone- or dual-APT without OAC therapy); DOAC, direct oral anticoagulant.

4.4.3 Factors associated with oral anticoagulant prescribing

Table 10 shows the results of the multivariate logistic regression analysis for factors associated with OAC prescribing in the pre-DOAC, post-DOAC, and overall study periods. Patients in the post-DOAC era were more likely to receive OAC therapy compared to patients in the pre-DOAC era (odds ratio [OR] 1.40, 95% CI 1.17 – 1.68, p < 0.001). Age was inversely associated with OAC prescribing in both eras and the entire study period. Conversely, male sex was

positively associated with OAC prescribing in the pre-DOAC era and overall study period. Higher stroke risk score (CHA_2DS_2-VASc $\geq$ 2) was significantly associated with OAC prescribing in both eras and for the entire study period. A history of prior bleeding, on the other hand, was inversely associated with OAC prescribing in both eras and the whole study period. Reasons for not prescribing an OAC were documented for 154 patients (Table 11). Falls risk, refusing OAC therapy, and adverse drug reactions, mainly recent bleeding from antithrombotic therapy were the most frequent reasons for not prescribing OACs.

Table 10. Factors associated with oral anticoagulant prescribing.

	Pre-DOAC era		Post-DOAC era		Overall Period	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age	0.98 (0.97 – 0.99)	0.025	0.98 (0.96 – 0.99)	0.048	0.98 (0.97 – 0.99)	< 0.001
Sex (reference = women)	1.34 (1.02 – 1.76)	0.031	1.19 (0.91 – 1.58)	0.198	1.28 (1.05 – 1.54)	0.012
Alcohol use	0.84 (0.51– 1.39)	0.491	0.79 (0.45 – 1.39)	0.411	0.82 (0.57 – 1.19)	0.299
Hypertension	1.43 (1.07 – 1.89)	0.013	1.17 (0.88 – 1.55)	0.276	1.21 (0.95 – 1.56)	0.114
Myocardial infarction	0.87 (0.58 – 1.30)	0.497	1.25 (0.80 – 1.99)	0.328	1.03 (0.77 – 1.39)	0.843
Congestive heart failure	1.83 (1.29 – 2.63)	0.001	1.14 (0.82 – 1.61)	0.432	1.36 (1.01 – 1.83)	0.042
Cerebrovascular diseases	1.62 (0.83 – 3.25)	0.161	0.86 (0.43 – 1.77)	0.631	1.16 (0.72 – 1.91)	0.540
Valvular heart diseases	2.25 (1.20 – 4.44)	0.014	1.33 (0.73 – 2.52)	0.362	1.71 (1.11 – 2.70)	0.017
Other embolic events *	1.58 (0.87 – 2.95)	0.139	1.25 (0.68 – 2.39)	0.477	1.42 (0.93 – 2.22)	0.108
Renal diseases	1.17 (0.71 – 1.96)	0.549	0.61 (0.36 – 1.02)	0.059	0.86 (0.60 – 1.23)	0.407

	Pre-DOAC era		Post-DOAC		Overall Period	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Diabetes mellitus	1.19 (0.87 – 1.65)	0.279	1.24 (0.89 – 1.73)	0.202	1.16 (0.90 – 1.49)	0.245
Ischaemic heart diseases	1.10 (0.83 – 1.46)	0.499	0.91 (0.68 – 1.24)	0.559	1.02 (0.83 – 1.25)	0.875
Stroke	1.52 (0.82 – 2.86)	0.188	1.20 (0.69 – 2.14)	0.520	1.34 (0.88 – 2.06)	0.167
Prior bleeding	0.15 (0.04 – 0.41)	< 0.001	0.17 (0.03 – 0.60)	0.015	0.14 (0.06 – 0.29)	< 0.001
CHA_2DS_2-VASc ≥ 2 vs. 0-1	1.72 (1.06 – 2.81)	0.030	2.16 (1.29 – 3.62)	0.004	1.95 (1.36 – 2.80)	< 0.001
HAS-BLED ≥ 3 vs. 0-2	1.06 (0.76 – 1.47)	0.747	1.63 (1.08 – 2.49)	0.022	1.23 (0.96 – 1.59)	0.107
DOAC era	–	–	–	–	1.40 (1.17 – 1.68)	< 0.001

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio.

* Include patients with history of deep venous thrombosis and pulmonary embolism.

Table 11. Summary of documented reasons for not prescribing an oral anticoagulant.

Reasons for not prescribing OAC	Pre-DOAC (n= 86)	Post-DOAC (n= 68)	p-value
Falls risk	36 (42%)	20 (29%)	0.154
Refusal	18 (21%)	14 (21%)	1.000
ADR (current bleeding)	14 (16%)	9 (13%)	0.765
Anaemia, thrombocytopaenia, clotting factor deficiencies, leukaemia	5 (6%)	6 (9%)	0.54
Non-compliance, labile INR	7 (8%)	8 (12%)	0.631
Aging, bipolar disorder, psychosis, dementia, renal failure, palliative care	4 (5%)	7 (10%)	0.216
Fear of bleeding, high bleeding risk, history of prior bleeding	2 (2%)	4 (6%)	0.406

ADR = adverse drug reaction; DOAC = direct oral anticoagulant; INR = international normalised ratio; OAC = oral anticoagulant.

4.5 Discussion

In this analysis, we noted a significant increase in OAC prescribing in the post-DOAC era. Most importantly, anticoagulation of high-risk patients significantly improved after DOACs began being subsidised by the Australian government. Widespread availability of DOACs after subsidisation (post-DOAC era) was an independent predictor of OAC prescribing, resulting in a 40% increase in the odds of a patient being prescribed an OAC after accounting for other factors. This increase was observed while the majority of our patients in both eras had high stroke risk scores requiring OAC therapy. Of note, baseline patient characteristics were broadly similar across the cohorts, particularly when comparing CHA_2DS_2-VASc and HAS-BLED scores that guide OAC prescribing.

There are two possible explanations for our findings. First, the availability of DOACs coupled with the relative efficacy, safety, and convenience associated with the use of the new agents compared to VKAs [288] could be the major driving factor for the increased OAC prescribing. Second, recent updates in AF guidelines including changes in the stroke risk scoring methods [9,19], increased awareness about AF, physicians becoming more familiar with stroke risk scoring methods [28], and promotion of DOACs by pharmaceutical companies in the Australian market are possible contributing factors for the overall increase in OAC prescribing.

One limitation of this study is that it involved hospitalised AF patients who could be relatively more comorbid than AF patients managed in primary care. Hence, our results may not reflect OAC prescribing rates in AF in the community setting. Moreover, this study was conducted in one referral hospital in the Southern Tasmania. However, the relatively large number of participants over an extended study period, and the study centre being the largest referral

hospital in the region can improve the robustness and representativeness of our study. Missing values and incomplete documentations inherent to observational studies were additional limitations. Nonetheless, our data clearly highlighted a fundamental improvement in OAC prescribing in the post-DOAC era, and that DOAC subsidisation was an independent predictor of OAC prescribing. This improvement could be considered as an essential step towards addressing the commonly reported issue of OAC underuse in patients with AF [95,269].

Overall OAC prescribing (56.5%) and anticoagulation of high-risk patients in the post-DOAC era was higher than an earlier study in Tasmania, which reported warfarin prescribing in 34% of AF patients with a high risk of stroke [289]. A more recent study from three Tasmanian hospitals indicated 52.5% OAC prescribing in high-risk patients with AF, lower than OAC prescribing rate in the post-DOAC era in our study [290]. The post-DOAC era anticoagulation rate in this study was comparable to a large observational data in the USA that showed 61.8% OAC prescribing among high-risk patients with AF [291]. However, our result was lower than two European registry studies: 70.9% OAC prescribing in high-risk patients in EORP-AF [278] and 85.6% in PREFER-AF [176].

Although anticoagulation of AF patients had improved in the post-DOAC era, OAC underuse in the high-risk and overuse in the low-risk groups was apparent in both eras. Furthermore, APT therapy was widely used among high-risk patients in both eras (38.9% and 28.2% in the pre- and post-DOAC eras, respectively). APT agents were prescribed more commonly in this study than in the PREFER-AF (12.2%) [176] and GLORIA-AF (10.0%) [270] registry studies. This is despite observational studies having demonstrated APT therapy in AF is less effective and no safer than OAC therapy [292]. A potential reason for the lower OAC and higher APT prescribing rates in this study compared to the European studies is the impact of guidelines.

Recently updated European AF guidelines no longer recommend APT agents in AF [76], however a current national guideline for the management of AF is lacking in Australia.

We also identified factors associated with OAC prescribing in the pre-DOAC, post-DOAC, and overall study period. Patients admitted in the post-DOAC era vs those admitted in the pre-DOAC era were more likely to receive an OAC. Conversely, our study confirmed the findings of prior studies that older age and perceived risk of bleeding were potent negative predictors of OAC prescribing in patients with AF [20]. In line with guideline recommendations, CHA_2DS_2-VASc ≥ 2 was a significant predictor of OAC prescribing in all the study periods. Despite studies demonstrating an increased stroke risk in females [125,293], males in the pre-DOAC era and overall study period had greater odds of being prescribed OACs than females. Nonetheless, women in our study population were older and at higher stroke risk than men (data not shown). Previous data from large observational studies also revealed lower odds of OAC prescribing in female patients with AF [291,294]. This may reflect under appreciation of gender as a risk factor for stroke in the practice settings despite guideline recommendations.

When documented reasons for not prescribing an anticoagulant were analysed, there was no significant difference in the frequency of stated reasons between the two eras. This suggests that the availability of DOACs has yet to change the way prescribers and patients think about OAC in AF. Our results were consistent with other studies that indicated aging, falls risk, physicians' fear of bleeding, and patients' abilities to comply with treatment as major barriers to OAC prescribing [295-297]. However, observational studies showed bleeding risk in aging and falling risk are overestimated and should not deter OAC prescribing in AF [298].

The present study provides empirical data regarding contemporary OAC prescribing in patients with AF now that the DOACs are feasible options in Australian clinical practice. This information is important given the limited studies regarding the impact of DOACs on Australian anticoagulation practices. Although there was an improvement in OAC prescribing, driven perhaps by the widespread availability of DOACs, the anticoagulation rate among high-risk patients in our study was lower than the rates reported in recent European studies [176,278]. While OAC underuse in high-risk patients persisted in the post-DOAC era, there was an apparent increase in OAC overuse in low-risk patients. Despite the widespread availability of DOACs, more than a third of high-risk patients without a contraindication to OAC therapy did not receive the therapy. Conversely, 42.9% of low-risk patients in the post-DOAC era received OAC therapy showing suboptimal use of risk stratification methods to determine OAC prescribing in AF. This suggests the need for further improvement towards optimal OAC prescribing for better stroke prevention in AF. Recent European AF guidelines recommend OAC for all patients with AF at moderate or high risk of stroke [76]. Widespread availability of DOACs [294,299], and increased awareness regarding AF [294,300] have improved OAC prescribing rates in Europe. Similar initiatives including national guideline development with a clear recommendation regarding OAC and APT prescribing in moderate-risk patients, interventions to strengthen adherence to guidelines, and education focusing on the importance of tailoring OAC to patients' stroke risk may have a role in optimising prescribing practices in Australia.

4.6 Conclusion

A significant increase in OAC prescribing was observed in the post-DOAC era, and the increment appeared to be largely driven by the availability of DOACs. However, OAC underuse in high-risk and overuse in low-risk patients was apparent throughout our study. These findings highlight the need to identify the drivers of anticoagulant under- and over-use and address them accordingly.

CHAPTER FIVE

5. Thromboembolism and mortality in the Tasmanian atrial fibrillation study.

Overview

This study aimed to address the third objective of the thesis. Results from the prior analyses (Chapters 3 and 4) indicated a progressive shift towards prescribing of DOACs and an overall increase in the prescribing of anticoagulants to patients with AF. The present analysis was built on the previous findings by focusing on investigating the impact of the general availability of DOACs on clinical outcomes (thromboembolism and all-cause mortality rates). It also compared outcomes between antithrombotic groups and identified factors that influenced the risk of incident thromboembolism and all-cause mortality in patients with AF. The results suggested a significant reduction in the incidence rates of embolic events and all-cause mortality in AF following general availability of DOACs. This study was published in *Cardiovasc. Pharmacol. Ther in July* 2018 *(https://www.ncbi.nlm.nih.gov/pubmed/29642709).*

5.1 Abstract

Background: While utilisation of anticoagulation in patients with atrial fibrillation (AF) has increased in recent years, contemporary data regarding thromboembolism and mortality incidence rates are limited outside of clinical trials. This study aimed to investigate the impact of direct oral anticoagulants (DOACs) on clinical outcomes of patients with AF included in the Tasmanian Atrial Fibrillation Study (TAFs).

Methods: The medical records of all patients with a primary or secondary diagnosis of AF who presented to public hospitals in Tasmania, Australia, between 2011 and 2015 were retrospectively reviewed. We investigated overall thromboembolic events (TEs), ischaemic stroke/transient ischaemic attack (IS/TIA), and mortality incidence rates in patients admitted to the Royal Hobart Hospital, the main teaching hospital in the state. We compared outcomes in two-time periods; prior to the availability of DOACs (pre-DOAC; 2011 to mid-2013), and following their general availability after Government subsidisation (post-DOAC; mid-2013 to 2015).

Results: Of the 2,390 patients with AF admitted during the overall study period, 942 patients newly prescribed an antithrombotic medication (465 and 477 from the pre-DOAC and post-DOAC time periods, respectively) were followed. We observed a significant decrease in the incidence rates of overall TE (3.2 vs 1.7 per 100 PY, $p < 0.001$) and IS/TIA (2.1 vs 1.3 per 100 PY, $p = 0.022$) in the post-DOAC compared to the pre-DOAC period. All-cause mortality was significantly lower in the post-DOAC period (2.9 vs 2.2 per 100 PY, $p = 0.028$). Increasing age, prior stroke, and admission in the pre-DOAC era were all risk factors for TE, IS/TIA, and

mortality in this study population. The risk of IS/TIA was more than doubled (HR 2.54, 95% CI 1.17-5.52) in current compared to ex- and non-smokers.

Conclusion: TE and all-cause mortality rates were lower following the widespread availability of DOACs in this population.

Key words: atrial fibrillation, anticoagulant, thromboembolism, ischaemic stroke, mortality.

5.2 Introduction

Atrial fibrillation (AF) increases the risk of thromboembolic events including ischaemic stroke, transient ischaemic attack (TIA), pulmonary embolism (PE), and myocardial infarction (MI), and significantly increases the risk of morbidity and mortality [154]. The association between AF and stroke is well-established. Population studies demonstrate that patients with AF have a 5-fold increase in their risk of stroke, and up to 25% of all patients with stroke have AF as their admission diagnosis [153,301]. Compared to AF-related stroke, less is known regarding the relationship between AF and other systemic embolic events (PE or deep venous thrombosis (DVT)) and MI. Observational data, however, show AF to be an important risk factor for these events [302,303]. A prospective cohort study by Soliman et al. involving 23,928 participants reported that AF was independently associated with a 2-fold increased risk of incident MI [304].

Epidemiological research shows that the prevalence of AF is rising globally [3,28]. This is likely to result in a substantial increase in hospital admissions and mortality due to AF-related cardiovascular complications in the future. Encouragingly, observational data from clinical practice and large AF registry studies have suggested that the proportion of patients with AF receiving OACs for stroke prevention is also increasing [176,305]. The major reasons for the growing rates of anticoagulation include the recent availability of DOACs [305], updated AF guidelines [9,177], and improved awareness about the importance of stroke prevention in AF [28,36].

DOACs were subsidised for stroke prevention in non-valvular AF in Australia in August 2013 in the hope that they would improve the clinical outcomes of patients and reduce the burden of AF-related stroke in the community. DOACs were rapidly adopted by prescribers, and by mid-

2015 almost 70% of anticoagulated patients with AF presenting to the Royal Hobart Hospital (RHH) received a DOAC [269,274]. The Tasmanian AF study (TAFs) was established in 2012 to monitor prescribing trends and patient outcomes in Tasmania, Australia, over time. Our previous analyses have focused on assessing the patterns of antithrombotic prescribing and the quality of anticoagulation practices in AF [284,305]. In this analysis, we aimed to investigate the impact of the availability of DOACs on the thromboembolic event (TE)-related readmissions of patients with AF. Our specific objectives were to: 1) compare thromboembolic and mortality rates in patients commenced on antithrombotic therapy prior to and following the availability of DOACs, and 2) identify factors that influenced the risk of incident thromboembolism and all-cause mortality in patients with AF.

5.3 Methods

5.3.1 Study design and participants

This was a retrospective observational study involving consecutive patients with AF admitted between 2011 and 2015 to the RHH, Tasmania, Australia. Patients were identified using the Australian Refined Diagnosis Related Groups, AR-DRG code-I48 for AF or flutter (referred to as AF hereafter). The Tasmanian Health and Medical Human Research Ethics Committee approved this study and informed consent was waived as the study was retrospective in nature and considered low risk. Patients' baseline demographics, comorbidities, and prescribed medications were obtained by reviewing digital medical records. Baseline stroke and bleeding risk scores were calculated using the CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 and Sex category-female) and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or

predisposition, Labile international normalised ratio (INR) - if documented in medical records, Elderly, Drugs or alcohol use > 8 drinks/week) scoring methods, respectively [125,127]. Labile INR was defined as an unstable or high INR (INR > 3) as recorded in the medical records. The Charlson Comorbidity Index (CCI) was used to quantify and compare comorbid conditions among groups [273]. The CCI, CHA_2DS_2-VASc, and HAS-BLED scores were estimated based on demographic variables and comorbidities diagnosed before or during index admissions. An index admission was defined as the participants' first hospitalisation to our study setting with AF as a primary or secondary diagnosis. Readmissions were subsequent hospitalisations after the index admission during the study period.

5.3.2 Follow-up and outcomes

To compare baseline characteristics, identify risk factors, and quantify incidence rates, patients were grouped according to the presence or absence of thromboembolism diagnosed at index admission or readmissions during follow-up. A TE was defined as a composite outcome including IS/TIA, other systemic embolic events (PE or DVT), and MI (ST-segment or non-ST elevation MI). Hospitalisations due to TEs were ascertained by reviewing the medical records where these comorbidities were documented as a primary or secondary diagnosis during the study period. Only the first TE was used in the analyses.

Analysis of TE and mortality incidence rates involved patients with AF newly initiated on an antithrombotic therapy at their index admissions. Exposure to an antithrombotic therapy at the discharge of index admissions was stratified according to the prescription of warfarin, DOACs, and APT agents (prescribed without an anticoagulant). For each patient, follow-up began immediately after treatment initiation and continued to the first TE, treatment change, treatment

discontinuation, in-hospital mortality, or end of the study period, whichever came first. For comparative purposes, we grouped study participants based on their index admission dates as follows: 1) pre-DOAC period - admissions between January 2011 and July 2013, and 2) post-DOAC period - admissions between August 2013 and July 2015. Finally, TE and all-cause in-hospital mortality incidence rates were also compared by treatment category initiated at the discharge of index hospitalisations.

5.3.3 Definitions of antithrombotic exposure, switch or discontinuation

Exposure to an antithrombotic (new initiation) was defined as discharge with an antithrombotic medication in patients with AF who did not have a documented history of being prescribed an antithrombotic prior to their index hospitalisation. We considered treatment to be discontinued when patients previously receiving thromboprophylaxis were discharged without any antithrombotic at subsequent readmissions, because of an emergence of contraindications, or without documented reasons, for an unspecified period. An antithrombotic switch was defined as a change from one type of antithrombotic to another that occurred during a readmission.

5.3.4 Statistical analysis

All statistical analyses were executed using R, version 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org/). Baseline patient characteristics were presented using descriptive statistics. Continuous variables were summarised as means and standard deviations (SD), and group differences were compared using *Analysis of variance* or independent samples *Student's t-tests*. Categorical variables were summarised as frequencies and proportions, and differences were tested using *Chi-square or Fisher exact-tests*, as appropriate.

We pooled IS/TIA, other systemic embolic events, and MI into a composite end point as overall TEs. Further, we pooled IS/TIA, and other systemic embolic events as another composite end point, and also completed an additional analysis for IS/TIA events only. The all-cause mortality incidence rate was estimated by following patients from the date of index hospitalisation to death or the end of the study period. For all outcomes, the first event after AF diagnosis was included regardless of whether the patient had a prior history of thromboembolism. However, all TEs occurring on the same day as AF diagnosis were excluded from the incidence analysis. Incidence rates and corresponding 95% confidence intervals (CIs) were calculated as the number of the first event in each category divided by the total patient-years (PY) at risk for a particular outcome within the observation period. All of the events were expressed as rates/100 PY of follow-up.

Cox proportional hazards regression analyses adjusted for baseline covariates were performed to identify risk factors for overall TE, IS/TIA, and all-cause mortality. The proportional hazards assumption was tested using *scaled Schoenfeld residuals* and was found appropriate for all the models. Risk relationships were presented as hazard ratios (HRs) and 95% CIs. $P < 0.05$ was considered statistically significant for all analyses.

5.4 Results

5.4.1 Patient demographics and clinical characteristics

During the study period (January 2011 to July 2015), we identified 2,390 patients with AF as a primary or secondary diagnosis. In total, 384 (16.1%) patients experienced thromboembolic complications during their index hospitalisation or at readmissions during follow-up; 264 (68.8%) had IS/TIA, 90 (23.4%) had MI, and 30 (7.8%) had other systemic embolic events including PE and DVT. Baseline characteristics of the overall study population and those admitted with thromboembolism are detailed in Table 12. Current smoking, hypertension, ischaemic heart disease, and a history of prior stroke were significantly more frequent in patients admitted with thromboembolic complications than those admitted due to other causes. Moreover, patients who experienced TEs were older (mean age 77.6 vs 74.2 years, $p < 0.001$), had higher stroke and bleeding risk scores (mean CHA_2DS_2VASc score 3.7 vs 3.1, and mean HAS-BLED score 2.5 vs 2.2, both $p < 0.001$) than patients who did not experience TEs.

Table 12. Baseline characteristics (overall and by thromboembolic events).

		TE-related admission		
Characteristics	All patients (n = 2390)	Yes[€] (n = 384)	No (n = 2006)	p-value
Age	75.1 (11.5)	77.6 (9.8)	74.2 (11.7)	< 0.001
Female	1068 (44.7)	166 (43.2)	902 (45.0)	0.568
Smoking history*	897 (38.1)	153 (39.9)	744 (37.1)	0.339
Current smoking	195 (8.2)	43 (11.2)	152 (7.6)	0.023
Alcohol (>8 units/week)	160 (6.7)	27 (7.0)	133 (6.6)	0.859
CCI, mean (SD)	4.4 (2.2)	4.6 (1.8)	4.4 (2.2)	0.193
Hypertension	1469 (61.5)	273 (71.1)	1196 (59.6)	< 0.001
Ischaemic heart disease	721 (23.9)	136 (35.4)	585 (29.2)	0.017
Diabetes mellitus	518 (21.7)	79 (20.6)	439 (21.9)	0.614
Chronic respiratory disease	495 (20.7)	64 (16.7)	431 (21.5)	0.039
Congestive heart failure	454 (19.0)	52 (13.5)	402 (20.0)	0.004
Chronic renal diseases	232 (9.7)	32 (8.3)	200 (10.0)	0.369
Valvular heart diseases	224 (9.4)	42 (10.9)	182 (9.1)	0.292
History of stroke	166 (6.9)	74 (19.3)	92 (4.9)	< 0.001
Previous embolic diseases[¥]	113 (4.7)	20 (5.2)	93 (4.6)	0.724

Characteristics	All patients (n = 2390)	TE-related admission		p-value
		Yes[€] (n = 384)	No (n = 2006)	
CHA_2DS_2-VASc, mean (SD)	3.2 (1.5)	3.7 (1.4)	3.1 (1.2)	< 0.001
CHA_2DS_2-VASc = 0	97 (4.1)	6 (1.6)	91 (4.5)	
CHA_2DS_2-VASc = 1	236 (9.9)	26 (6.8)	210 (10.5)	
CHA_2DS_2-VASc ≥ 2	2057 (86.1)	352 (91.7)	1705 (85.0)	
HAS-BLED, mean (SD)	2.2 (0.7)	2.5 (0.8)	2.2 (0.7)	< 0.001

Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation; TE, thromboembolic event. *Includes current and ex-smokers. [€] Includes thromboembolic event (stroke/transient ischaemic attack, systemic embolism and myocardial infarction) diagnosed at index admission or readmissions. [¥]Includes patients with history of deep venous thrombosis and pulmonary embolism.

5.4.2 Thromboembolic and mortality incidence rates

Thromboembolic and mortality incidence rates categorised by admission eras and treatment groups are presented in Tables 13 and 14, respectively. A total of 942 patients (465 from the pre-DOAC and 477 from the post-DOAC era) newly initiated on antithrombotic therapy at their index admission were included for this analysis. The mean follow-up duration for the pre- and post-DOAC cohorts were 1,204 and 863 PY, respectively. Overall, 54 patients (39 from the pre-DOAC and 15 from the post-DOAC time periods) experienced TE during follow-up.

A significant reduction was observed in the incidence rates of overall TEs, TE/TIA or systemic embolic events, IS/TIA events, and all-cause mortality in the post-DOAC compared to the pre-

DOAC era. During follow-up, TE occurred in 39 patients in the pre-DOAC and 15 patients in the post-DOAC group (3.2 vs 1.7 per 100 PY, p <0.001). Combined IS/TIA or other systemic embolic events occurred in 29 patients in the former and 13 patients in the later period (2.4 vs 1.5 per 100 PY, P = 0.014). Similarly, IS/TIA events occurred in 25 and 11 patients in the pre- and post-DOAC groups, respectively (2.1 vs 1.3 per 100 PY, p = 0.022). Furthermore, the incidence rate of all-cause mortality was significantly lower in the post-DOAC era than in the pre-DOAC era (2.9 vs 2.2 per 100 PY, p = 0.028).

When TE incidence rates were analysed by antithrombotic prescribing at the discharge of the index hospitalisations, lower rates of overall TE and combined IS/TIA or other systemic embolic events were observed in patients initiated on DOACs than in the warfarin and APT only cohorts. Mean follow-up durations by treatment category were: 894 PY for warfarin, 208 PY for DOACs, and 488 PY for APT agents. The overall TE incidence rates per 100 PY were: 3.2 in the warfarin, 1.9 in the DOAC, and 4.3 in the APT agent groups (p = 0.002 for the group comparison). Moreover, IS/TIA or other systemic embolism incidence rates per 100 PY were: 2.6 in the warfarin, 1.9 in the DOAC, and 3.1 in the APT agent groups (p = 0.027 for the group comparison).

Table 13. Thromboembolism and all-cause mortality incidence rates in patients with atrial fibrillation by admission era.

	Pre-DOAC era (n = 465)		Post-DOAC era (n = 477)		
	Event	Rate per 100 PY (95% CI)	Event	Rate per 100 PY (95% CI)	p value
Overall TEs[¥]	39	3.2 (2.3 – 4.4)	15	1.7 (1.0 – 2.9)	< 0.001
IS/TIA or SE	29	2.4 (1.6 – 3.5)	13	1.5 (0.8 – 2.6)	0.014
IS/TIA	25	2.1 (1.4 – 3.1)	11	1.3 (0.7 – 2.3)	0.022
MI	10	0.8 (0.4 – 1.6)	2	0.2 (0.0 – 0.9)	0.038
SE*	4	0.3 (0.1 – 0.9)	2	0.2 (0.0 – 0.9)	0.446
Fatal stroke/TIA	5	0.4 (0.1 – 1.0)	4	0.5 (0.2 – 1.4)	0.750
All-cause morality	35	2.9 (2.1 – 4.1)	19	2.2 (1.4 – 3.5)	0.028

Abbreviations: TEs, thromboembolic events; IS, ischaemic stroke; TIA, transient ischaemic attack; SE, systemic embolic event; MI, myocardial infarction; DOAC, direct oral anticoagulant; PY, patient-years; CI, confidence interval. * Includes other systemic embolic diseases such as deep venous thrombosis and pulmonary embolism. [¥] Includes ischaemic stroke/transient ischaemic attack, systemic embolism and myocardial infarction.

Table 14. Thromboembolism incidence rates by antithrombotic therapy.

	Warfarin (N=431)		DOAC (N=258)		Antiplatelet (n = 253)		
Variable	Events	Rate per 100 PY (95% CI)	Events	Rate per 100 PY (95% CI)	Events	Rate per 100 PY (95% CI)	p value
Overall TE¥	29	3.2 (2.2 – 4.7)	4	1.9 (0.6 – 5.2)	21	4.3 (2.7 – 6.6)	0.002
IS/TIA or SE	23	2.6 (1.7 – 3.9)	4	1.9 (0.6 – 5.2)	15	3.1 (1.8 – 5.1)	0.027
IS/TIA	20	2.2 (1.4 – 3.5)	4	1.9 (0.6 – 5.2)	12	2.5 (1.3 – 4.4)	0.082
MI	6	0.7 (0.3 – 1.5)	0	0.0	6	1.2 (0.5 – 2.8)	0.060
SE*	3	0.3 (0.1 – 1.1)	0	0.0	3	0.6 (0.2 – 1.9)	0.217
Fatal stroke	5	0.5 (0.2 – 1.4)	0	0.0	4	0.8 (0.3 – 2.2)	0.114

Abbreviations: DOAC, direct oral anticoagulant; TE, thromboembolic event; IS, ischaemic stroke; TIA, transient ischaemic attack; MI, myocardial infarction; SE, systemic embolism; PY, patient-years; CI, confidence interval. * Includes other systemic embolic diseases such as deep venous thrombosis and pulmonary embolism. ¥ Includes ischaemic stroke/transient ischaemic attack, systemic embolism and myocardial infarction.

5.4.3 Factors that influenced the risk of thromboembolism and mortality

Table 15 summarises Cox regression analysis results for the risk factors associated with overall TEs (IS/TIA, other systemic embolic events, MI), IS/TIA, and all-cause mortality. After adjusting for baseline covariates, independent risk factors associated with the incidence of overall TEs were: increasing age (HR 1.03, 95% CI 1.01–1.05), hypertension (HR 1.81, 95% CI 1.08 – 3.46), history of prior stroke (HR 2.56, 95% CI 1.08 – 5.22), and MI (HR 1.17, 95% CI 1.05 – 1.68). Furthermore, admission in the pre-DOAC era (relative to admission in the post-DOAC era) was also significantly associated with an incident risk of TE (HR 1.21, 95% CI 1.02 –1.84).

Independent risk factors for incident IS/TIA included increasing age (HR 1.04, 95% CI 1.01 – 1.07), current smoking (HR 2.54, 95% CI 1.17 – 5.52), hypertension (HR 2.63, 95% CI 1.42 – 4.26), prior stroke (HR 3.57, 95% CI 1.57 – 5.12), and hospitalisation in the pre-DOAC era (HR 1.42, 95% CI 1.02 – 2.37). Finally, risk factors independently associated with the incidence of all-cause mortality included: increasing age (HR 1.06, 95% CI 1.03 – 1.09), chronic renal diseases (HR 2.51, 95% CI 1.18 – 5.34), prior stroke (HR 2.47, 95% CI 1.11 – 5.48), MI (HR 2.62, 95% CI 1.38 – 4.98), and admission in the pre-DOAC era (HR 1.30, 95% CI 1.07 – 2.36). Sex category, alcohol use (> 8 units /week, as documented on the patients' medical records), a history of congestive heart failure, diabetes mellitus, chronic respiratory disease, ischaemic heart disease, valvular heart diseases, and other systemic embolic events were not significantly associated with the risk of overall TEs, IS/TIA, and all-cause mortality in this study population.

Table 15. Factors that influenced the risk of thromboembolism and all-cause mortality.

	Overall TEs		IS/TIA		All-cause mortality	
Characteristics	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1.01 – 1.05)	0.026	1.04 (1.01 – 1.07)	0.023	1.06 (1.03 – 1.09)	< 0.001
Women	0.83 (0.42 – 1.42)	0.493	0.64 (0.35 – 1.20)	0.167	1.23 (0.71 – 2.14)	0.463
Smoking history*	1.41 (0.82 – 2.40)	0.211	1.51 (0.81 – 2.82)	0.191	2.54 (0.97 – 2.82)	0.066
Current smoking	2.04 (0.99 – 4.17)	0.051	2.54 (1.17 – 5.52)	0.018	1.03 (0.41 – 2.59)	0.146
Alcohol	0.99 (0.36 – 2.75)	0.988	0.32 (0.04 – 2.34)	0.262	0.99 (0.36 – 2.77)	0.298
Hypertension	1.81 (1.08 – 3.46)	0.035	2.63 (1.42 – 4.26)	0.007	1.05 (0.60 – 1.86)	0.854
Ischaemic heart disease	1.33 (0.76 – 2.32)	0.318	0.91 (0.46 – 2.86)	0.836	1.14 (0.64 – 1.81)	0.663
Diabetes mellitus	0.61 (0.28 – 1.36)	0.228	0.46 (0.16 – 1.30)	0.143	1.42 (0.77 – 2.61)	0.261
Chronic respiratory disease	0.84 (0.41 – 1.72)	0.637	1.06 (0.49 – 2.29)	0.890	1.44 (0.78 – 2.64)	0.244

	Overall TEs		**IS/TIA**		**All-cause mortality**	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Congestive heart failure	1.60 (0.82 – 3.11)	0.164	1.32 (0.58 – 2.99)	0.503	1.75 (0.92 – 3.33)	0.087
Chronic renal diseases	0.57 (0.14 – 2.37)	0.445	0.79 (0.19 – 3.29)	0.749	2.51 (1.18 – 5.34)	0.016
Valvular heart disease	1.18 (0.47 – 2.98)	0.718	1.28 (0.45 – 3.61)	0.641	0.97 (0.35 – 2.69)	0.152
History of stroke/TIA	2.56 (1.08 – 5.22)	0.021	3.57 (1.57 – 5.12)	0.002	2.47 (1.11 – 5.48)	0.026
Myocardial infarction	1.17 (1.05 – 1.68)	0.043	1.31 (0.51 – 3.36)	0.567	2.62 (1.38 – 4.98)	0.003
Previous embolic disease[¥]	1.48 (0.46 – 4.75)	0.509	0.65 (0.09 – 4.72)	0.668	1.46 (0.56 – 4.68)	0.524
Pre-DOAC era	1.21 (1.02 – 1.84)	0.025	1.42 (1.02 – 2.37)	0.017	1.30 (1.07 – 2.36)	0.039

Abbreviations: TEs, thromboembolic events; IS, ischaemic stroke; TIA, transient ischaemic attack; HR, hazard ratio; CI, confidence interval; *Includes current and ex-smokers. [¥] Pulmonary embolism, deep venous thrombosis.

5.5 Discussion

This study provides a comprehensive description of patients with AF admitted with TEs, identifies risk factors, and compares TE and all-cause mortality incidence rates prior to and following the introduction of DOACs into clinical practice. We observed a significant reduction in the incidence rates of TEs and all-cause mortality in patients with AF following the Government subsidisation of DOACs. TE incidence rates were also lower in patients initiated on DOACs compared to those initiated on warfarin and APT agents at index admissions. Furthermore, hospitalisation post-DOAC availability was associated with a decreased risk of overall TEs, IS/TIA, and all-cause mortality. This was despite the similarity in the baseline characteristics of the study participants newly initiated on antithrombotic therapies, particularly when we compared baseline stroke risk scores between the two time-periods (Supplementary Table 16). The declining rates of TEs, IS/TIA, and total mortality in this analysis were consistent with findings that showed a declining trend of stroke and mortality incidence rates in AF reported from other countries [306-308].

The explanations for these findings are likely multifactorial. First, changes in clinical practice such as increasing rates of OAC prescribing in recent years, driven mainly by the availability of DOACs, and updates in AF management guidelines, could have improved patient outcomes. A recent analysis of OAC prescribing in AF in the same population showed the proportion of patients with AF receiving OACs increased significantly over the study period [284,290]. Second, DOACs are increasingly used in patients with non-valvular AF in preference to warfarin [305,309]. Comparative analysis involving warfarin-treated patients in this study also indicated no significant difference in the overall TE, IS/TIA, and all-cause mortality incidence rates between the two eras (data not shown). This suggests the observed improvements in

clinical outcomes were potentially due to the increasing utilisation of DOACs in patients with AF rather than improvements in warfarin management. Based on trial results, this is expected to result in fewer complications such as ICH or other major bleeding events. Clinical trials demonstrated lower rates of major bleeding and mortality in patients treated using DOACs compared to those receiving warfarin [99,100]. In addition, observational data has shown that all DOACs reduced intracerebral bleeds, the most feared complication of OAC therapy in patients with AF, by at least 50% [310]. Meta-analysis studies also reported a significant decline in IS/systemic embolism and total mortality that appeared to be driven by a reduction in fatal bleeding in DOAC- compared to warfarin-treated patients [311-313].

Although randomised clinical trials and the majority of observational data showed comparable efficacy between DOACs and warfarin in terms of stroke prevention, few studies indicated lower rates of thromboembolism in patients treated with DOACs than those treated with warfarin [314]. A real-world practice study among Asians with non-valvular AF reported a lower risk of IS/systemic embolism and all-cause mortality in patients with AF receiving dabigatran and rivaroxaban compared with patients receiving warfarin [315]. Moreover, other factors such as improved management of chronic diseases including hypertension, congestive heart failure, and diabetes mellitus could also play significant roles in the reduction of TE and mortality incidence rates in AF.

AF-related TE rates in cohort studies are highly heterogeneous and have ranged from 0.45 to 9.28 per 100 PY owing to variabilities in the study design, study setting, and the data source [316]. While low overall TE and IS/TIA incidence rates were observed in patients initiated on DOACs in this study, IS/TIA incidence rates in patients initiated on warfarin in this study were broadly similar to rates reported from large observational studies in Europe and Japan [317-

319]. Our analysis showed comparable rates of IS/TIA and other systemic embolic events, but a lower rate of all-cause mortality than rates reported from a large nationwide observational study in Denmark [317]. Furthermore, no MI were observed in patients initiated on DOACs while the incidence rate of MI in patients initiated on warfarin in this analysis corresponded with a 0.7 per 100 PY MI rate in AF patients who received warfarin in the United Kingdom [318].

The risk of stroke in patients with AF is high and increases in the presence of other risk factors, particularly those described in the validated CHA_2DS_2-VASc stroke risk score [125]. However, the contribution of some of these factors may underestimate the true risk of stroke in the real-world patient management. For instance, a history of prior stroke is the most prominent risk factor for IS/TIA in AF, and the contribution of prior stroke in predicting IS/TIA recurrence is considered to be higher than that described in the CHA_2DS_2-VASc score [320,321]. Although existing evidence is not robust, other comorbidities and demographic factors not included in the CHA_2DS_2VASc score such as chronic renal diseases and smoking could be important risk factors for thromboembolism in AF. Our study builds on the available data by comparing previously reported risk factors and identifying concomitant comorbidities as additional risk factors for TE and mortality in contemporary patients with AF.

The strongest risk factors for the overall TE and IS/TIA outcome used in this study were a history of stroke, followed by hypertension, admission in the pre-DOAC era, and increasing age. Patients with a history of prior IS/TIA had a more than 2-fold increase in the risk of overall TE and all-cause mortality, and more than 3-fold increase in the risk of recurrent IS/TIA than patients without a history of prior IS/TIA. Previous studies also showed a history of prior stroke as the most powerful and consistent risk factor for recurring cerebrovascular events in AF

[321,322]. Current smoking was also identified as an important risk factor for IS/TIA in our analysis; the risk of suffering an IS/TIA was more than doubled (HR 2.54, 95% CI 1.17 – 5.52) in current smokers over non-smokers and former smokers. Similarly, an observational study involving optimally anticoagulated patients with AF found an independent association between smoking and IS/TIA [320].

The Framingham Heart Study also showed the risk of stroke in heavy smokers (> 40 cigarettes/day) was twice that of light smokers (< 10 cigarettes/day), whereas stroke risk decreased significantly two years after smoking cessation [323]. Evidence from pathological data and clinical research established that smoking causes mainly atherothrombotic strokes, as opposed to cardioembolic strokes due to AF [324,325]. Such strokes are shown to be effectively treated by APT therapy in preference to OAC therapy [326,327]. Further studies should investigate the differential relationship of smoking with the risk of cardioembolic stroke, and outcomes of OAC vs APT therapy in smoking patients with AF.

Patients with advanced age, chronic renal diseases, prior IS/TIA, MI, and hospitalisation in the pre-DOAC era (relative to the later period) were significant risk factors for all-cause mortality in this study. Similarly, a meta-analysis study by Gomez-Outes et al. revealed that IS/TIA and bleeding accounted for 6% of all deaths, with aging and decreased creatinine clearance as significant risk factors for mortality in patients with AF. Unlike our data, however, congestive heart failure, diabetes mellitus, and male sex were also significant risk factors for mortality in their study [328]. In conclusion, our data suggests that, in addition to optimal anticoagulation of patients with AF, effective control of modifiable risk factors such as smoking and management of comorbidities are essential to further reducing thrombosis and mortality in patients with AF.

The major strength of our study is that we include a relatively large number of participants over an extended observation period comprising admissions form both the pre- and post-DOAC time periods. However, given the observational nature of our data, there are a number of limitations. First, there is a potential for selection bias inherent to retrospective observational studies; exposure to antithrombotic therapy at index admissions was not randomised. Second, we were not able to capture TEs resulting in readmission to other clinical settings, minor events managed in local general practices, severe thromboembolic complications leading to pre-hospital death or death occurring outside our study setting. This may underestimate the overall TE and mortality incidence rates observed in this study. Third, as the study population was hospitalised AF patients, incidence rates may not reflect clinical outcomes of AF populations managed in community settings. Fourth, despite statistical adjustments, there is always a possibility of residual confounding limiting our ability to draw causal inferences. Moreover, adherence to OAC therapy and its impact on patient outcome was not assessed in this study population. Lastly, the number of patients who experienced MI and other systemic embolism in both time periods was small.

5.6 Conclusion

In this contemporary cohort of hospitalised patients with AF, the incidence rates of TE and all-cause mortality improved significantly following the introduction of DOACs. These improved clinical outcomes are likely to be multifactorial, potentially including the recent increase in OAC prescribing, and the use of DOACs in preference to warfarin. Patients with a history of stroke, increasing age, and admissions in the pre-DOAC era were most vulnerable to incident TEs, IS/TIA and all-cause mortality in this population. Furthermore, the risk of IS/TIA was more than doubled in current smokers compared to ex- and non-smokers. The results suggest

there are further opportunities to improve patient outcomes through judicious use of OACs, effective management of comorbidities, and controlling modifiable stroke risk factors.

Table 16 (Supplementary). Baseline characteristics of patients newly initiated on antithrombotic therapies by admission era.

Characteristics	Pre-DOAC era (n = 465)	Post-DOAC era (n = 477)	p-value
Age, mean (SD)	74.1 (11.5)	73.1 (10.7)	0.352
Women	189 (40.6)	219 (45.9)	0.117
Smoking history*	195 (41.9)	169 (35.4)	0.047
Current smoking	43 (9.2)	48 (10.1)	0.754
Alcohol (>8 units/week)	33 (7.1)	37 (7.8)	0.793
CCI, mean (SD)	4.3 (2.1)	4.1 (2.2)	0.249
Hypertension	323 (69.5)	278 (58.3)	0.001
Ischaemic heart disease	155 (33.3)	107 (22.4)	< 0.001
Diabetes mellitus	98 (21.1)	99 (20.7)	0.967
Chronic respiratory disease	95 (20.4)	95 (19.9)	0.908
Congestive heart failure	68 (14.6)	73 (15.3)	0.840
Renal diseases	30 (6.4)	42 (8.8)	0.216
Valvular heart diseases	38 (8.2)	29 (6.1)	0.262
History of stroke	19 (4.1)	44 (9.2)	0.002
Peptic ulcer diseases	36 (7.7)	14 (2.9)	0.002
Previous embolic diseases¥	21 (4.5)	21 (4.4)	1.000

Characteristics	Pre-DOAC era	Post-DOAC era	p-value
CHA_2DS_2-VASc, mean (SD)	3.1 (1.5)	3.1 (1.6)	0.708
HAS-BLED, mean (SD)	2.2 (0.7)	2.1 (0.8)	0.656

Abbreviations: DOAC, direct oral anticoagulant; CCI, Charlson comorbidity index; SD, standard deviation; *Includes current and ex-smokers. ¥Includes patients with history of deep venous thrombosis and pulmonary embolism.

CHAPTER SIX

6. Bleeding-related remissions in patients with atrial fibrillation receiving antithrombotic therapy: results from the Tasmanian atrial fibrillation study.

Overview

This analysis aimed to address the fourth objective of the thesis, i.e. to quantify and compare bleeding rates among patients newly initiated on antithrombotic therapies (warfarin, DOACs, APT agents), and identify factors associated with bleeding. The results showed low overall and major bleeding rates relative to other observational data. The rate of major bleeding was lower in DOAC- than warfarin-treated patients. Increasing age, a history of prior bleeding, treatment using warfarin, and multiple antithrombotic therapies were independent predictors of bleeding. Our findings suggested that stroke prevention using DOACs, in preference to warfarin, and avoiding multiple antithrombotic therapies, especially in the elderly patients with AF, have the potential to reduce bleeding events. This analysis was published in the European Journal of Clinical Pharmacology in December 2017, (https://www.ncbi.nlm.nih.gov/pubmed/28939954).

6.1 Abstract

Background and aims: Limited data is available from the Australian setting regarding bleeding in patients with atrial fibrillation (AF) receiving antithrombotic therapy. We aimed to investigate the incidence of hospital admissions due to bleeding and factors associated with bleeding in patients with AF who received antithrombotic therapy.

Methods: A retrospective cohort study was conducted involving all patients with AF admitted to the Royal Hobart Hospital, Tasmania, Australia, between January 2011 and July 2015. Bleeding rates were calculated per 100 patient-years (PY) of follow-up, and multivariable modelling was used to identify predictors of bleeding.

Results: Of 2,202 patients receiving antithrombotic therapy, 113 presented to the hospital with a major or minor bleeding event. These patients were older, had higher stroke and bleeding risk scores, and were more often treated with warfarin and multiple antithrombotic therapies than patients who did not experience bleeding. The combined incidence of major and minor bleeding was significantly higher in warfarin- versus DOAC- and APT-treated patients (4.1 vs 3.0 vs 1.2 per 100 PY, respectively; $p = 0.002$). Similarly, the rate of major bleeding was higher in patients who received warfarin than in the DOAC and APT cohorts (2.4 vs 0.4 vs 0.6 per 100 PY, respectively; $p = 0.001$). In multivariate analysis, increasing age, prior bleeding, warfarin, multiple antithrombotic therapy and high HAS-BLED scores were independently associated with bleeding.

Conclusion: The overall rate of bleeding in this cohort was low relative to similar observational studies. The rate of major bleeding was higher in patients prescribed warfarin compared to DOACs, with a similar rate of major bleeding for DOACs and APT agents. Our

findings suggest potential strategies to reduce bleeding include using DOACs in preference to warfarin, and avoiding multiple antithrombotic therapy in patients with AF.

Key words: atrial fibrillation, anticoagulant, bleeding, antithrombotic reversal.

6.2 Introduction

Atrial fibrillation (AF) is a major risk factor for stroke and judicious use of OACs is essential in its management. Bleeding events, however, are common complications of OAC therapy in patients with AF [329]. Major bleeding during OAC therapy is associated with high morbidity and mortality [330,331]. Minor bleeding events also have prognostic importance as they frequently lead to major bleeding, interruption of antithrombotic therapy, ischaemic stroke, and death [332]. In recent years, antithrombotic therapies have been increasingly used in patient groups at higher risk of bleeding [333]. This trend appears to be driven by improved AF screening practices [28,334], changes to AF treatment guidelines [9,10], and the availability of DOACs in clinical practice [269]. Moreover, observational studies showed hospitalisation due to antithrombotic-associated bleeding are increasing [335,336].

DOACs became available in Australian clinical practice in 2011 with the uptake of the new agents increasing rapidly following their listing on the Australian Pharmaceutical Benefits Scheme (PBS) for subsidy by the government in August and September 2013 [309]. Nonetheless, little is known regarding characteristics of patients experiencing bleeding, and the comparative frequency of bleeding in patients with AF receiving DOACs, warfarin, and APT agents in the Australian clinical setting. In this study, we aimed to investigate: 1) the characteristics of patients with AF admitted with bleeding, 2) bleeding rates among patients newly initiated on antithrombotic therapies, and 3) factors associated with bleeding in patients with AF receiving antithrombotic therapy.

6.3 Methods

6.3.1 Study design

The Tasmanian Atrial Fibrillation (TAF) study is a retrospective cohort study, which followed patients with AF who were admitted to public hospitals in Tasmania, Australia between 2011 and 2015. The aims and methods of the TAF study have previously been described [137,284]. For this analysis, all patients diagnosed with AF (Australian Redefined Diagnosis Related Groups, AR-DRG code I48), and admitted to the Royal Hobart Hospital (RHH) between January 2011 and July 2015 were included. The RHH is the largest referral hospital in Tasmania, and services a population of approximately 240,000 people in the south of the State. An index admission was defined as the patients' first admission, with AF as a primary or secondary diagnosis, and readmissions were subsequent admissions after the index admission during our study period.

6.3.2 Patient demography and comorbidities

Demographic and medical data were obtained from the patients' digital medical records and entered into an online database. Stroke risk score was calculated using the CHA_2DS_2-VASc (one point each for Congestive heart failure, Hypertension, Diabetes mellitus, Vascular diseases, Sex category-females, Age 65-74 years, and two points for Age $\geq$ 75 years and Stroke or transient ischaemic attack) method [125]. Bleeding risk was calculated using HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR (if documented), Elderly age > 65 years, Drugs/APT agents, nonsteroidal anti-inflammatory drugs or alcohol use > 8 units/week) method [127]. The Charlson Comorbidity Index (CCI) was calculated to compare comorbidity [273].

6.3.3 Readmissions and cohorts

Patients who received antithrombotic medications (warfarin, DOACs, APT agents, heparin or derivatives) before, during, or at discharge of their index admission were reviewed retrospectively for bleeding-related hospitalisation. Major bleeding was defined according to the criteria of the International Society of Thrombosis and Haemostasis (ISTH) [337] as fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial, intraocular, retroperitoneal, intraspinal, intra-articular), bleeding causing a decrease in haemoglobin level ≥ 20 g/L, or documented transfusion of at least 2 units of whole blood or red blood cells (RBC). Minor bleeding included events such as epistaxis, haematuria, or other bleeding events not under the definition of major bleeding.

To summarise and compare patient characteristics, patients were grouped according to the presence or absence of antithrombotic-related bleeding diagnosed at index admission or readmissions during the study period. The combined rate of bleeding events included both major and minor bleeding events diagnosed at index admission or readmissions. Only the first bleeding event was used to assess patient characteristics, and identify factors associated with bleeding. Analysis of the bleeding incidence rate was limited to patients newly initiated on antithrombotic therapies in three groups: i) warfarin, ii) DOACs (with or without APT therapy for both groups), and iii) single or dual-APT therapy. Subjects were followed from treatment initiation to the first bleeding event, treatment discontinuation, antithrombotic switch, death or end of the study period, whichever occurred first.

6.3.4 Statistical analysis

Baseline characteristics and treatment related information of patients with and without bleeding were presented using descriptive statistics. Continuous variables were presented as mean $\pm$ standard deviations and categorical variables as frequencies and percentages. Comparative analyses were performed using the independent sample *t-test and chi-square or Fisher's exact test*, as appropriate. The incidence rates of bleeding (combined, major, and minor bleeding) were calculated as the number of first bleeding events divided by the total time at risk for bleeding within the study period. Bleeding incidence rates were expressed as rates/100 patient-years (PY) of follow-up. We calculated early bleeding rates by dividing bleeding events occurring within 90 days of follow-up after initiating therapy by the total time at risk of patients within three months.

We used Kaplan-Meier curves to present the cumulative incidence of bleeding and the survival-free rates between treatment groups were compared using the long-rank test. Multivariate logistic regression adjusted for a set of baseline variables was used to identify independent predictors of bleeding. We followed a purposeful selection of covariates and variables having a significant univariate test ($p < 0.25$) were included in the multivariate model. Collinearity among predictor variables was checked using the variance inflation factor (VIF), and variables with VIF ≤ 3 were included in the final model. All statistical analyses were conducted using R, version 3.2.5 and SPSS, version 23. A p-value < 0.05 was considered statistically significant.

6.4 Results

6.4.1 Baseline patient characteristics

Among the 2,202 patients with AF who received antithrombotic therapy, a bleeding event occurred in 113 patients, of whom 68 (60.2%) and 45 (39.8%) had major and minor bleeding events, respectively. The overall event rates were 5.1%, 3.1% and 2.0% for any bleeding-related event, major bleeding and minor bleeding, respectively. The most frequent bleeding event by bleeding site was gastrointestinal (38.9%) followed by intracranial haemorrhage (ICH) (36.3%), while bleeding events from other sites accounted for 24.8% of cases. Bleeding was fatal in 14 (12.4%) patients; all of these patients suffered an ICH. The baseline characteristics of patients admitted due to bleeding or other causes are summarised in Table 17.

There was no significant difference in the frequency of most characteristics between the two groups. However, patients with bleeding were older, suffered greater comorbidity (mean CCI score 4.9 vs 4.5, $p = 0.047$) and had higher stroke and bleeding risk scores (mean CHA_2DS_2-VASc score 3.6 vs 3.3, $p = 0.022$, and mean HAS-BLED score 2.7 vs 2.3, $p < 0.001$, respectively) than patients who did not experience bleeding. Compared with those admitted for other reasons, patients admitted with bleeding were more frequently treated with warfarin and multiple antithrombotic therapies at index admission.

Table 17. Baseline characteristics of study population by bleeding status.

Characteristics		Antithrombotic-related bleeding		
		Yes (n = 113)	No (n = 2089)	p-value
Demographics	Age, mean (SD)	78.9 (8.4)	75.2 (11.0)	< 0.001
	Sex, females, n (%)	42 (37.2)	923 (44.2)	0.172
	Smoking *, n (%)	38 (33.6)	796 (38.1)	0.392
	Alcohol (> 8 units/week)	6 (5.3)	142 (6.8)	0.673
Comorbidities	Hypertension	65 (57.5)	1321 (63.2)	0.261
n (%)	Ischaemic heart diseases	38 (33.6)	665 (31.8)	0.768
	Diabetes mellitus	29 (25.7)	469 (22.4)	0.497
	Congestive heart failure	22 (19.5)	409 (19.6)	1.000
	Myocardial infarction	17 (15.0)	239 (14.4)	0.311
	Valvular heart disease	14 (12.4)	204 (9.8)	0.454
	Renal diseases	13 (11.5)	206 (9.9)	0.684
	History of stroke	10 (8.8)	150 (7.2)	0.631
	Cerebrovascular disease	8 (7.1)	123 (5.9)	0.751
	History of bleeding	6 (6.2)	31 (1.5)	0.010
	Peripheral vascular disease	3 (2.6)	84 (4.0)	0.623
CCI, mean (SD)		4.9 (1.9)	4.5 (2.1)	0.047

Characteristics		Antithrombotic-related bleeding		p-value
		Yes (n = 113)	No (n = 2089)	
CHA_2DS_2-VASc, mean (SD)		3.6 (1.5)	3.3 (1.5)	0.022
HAS-BLED score, mean (SD)		2.7 (0.8)	2.3 (0.7)	< 0.001
Antithrombotic at index admission	Warfarin	79 (69.9)	900 (43.1)	< 0.001
	DOAC	19 (16.8)	382 (18.3)	
	APT	15 (13.3)	729 (34.9)	
	Multiple antithrombotic ¥	39 (34.5)	437 (20.9)	< 0.001

Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation; ***** Includes current and ex-smokers. ¥ Includes patients receiving oral anticoagulant-APT or dual antiplatelet combination therapy.

6.4.2 Factors associated with bleeding

The factors independently associated with bleeding are summarised in Table 18. After adjusting for baseline characteristics, increasing age, a history of prior bleeding, warfarin (vs DOACs and APT agents), and multiple antithrombotic therapy (vs single antithrombotic therapy) were independently associated with bleeding events. The factors most strongly associated with bleeding were a history of prior bleeding (odds ratio [OR] 3.25, 95% CI 1.12-8.19), warfarin therapy (OR 2.47, 95% CI 1.46-4.41), and multiple antithrombotic therapy (OR 2.45, 95% CI 1.61-3.71).

Table 18. Predictors of hospitalisation due to antithrombotic-related bleeding.

	Unadjusted		Adjusted	
Factors	OR (95% CI)	p-value	OR (95% CI)	p–value
Age	1.04 (1.02-1.06)	< 0.001	1.05 (1.03-1.08)	0.001
Sex (males)	1.34 (0.91-1.99)	0.144	1.53 (1.00-2.36)	0.051
Smoking* (Yes)	0.82 (0.55-1.22)	0.340		
Alcohol (> 8 units/week)	0.77 (0.30-1.64)	0.539		
Hypertension	0.79 (0.54-1.17)	0.222	0.68 (0.45-1.02)	0.062
Ischaemic heart diseases	1.08 (0.72-1.61)	0.690		
Diabetes mellitus	1.19 (0.76-1.82)	0.427		
Congestive heart failure	0.99 (0.61-1.57)	0.977		
Myocardial infarction	1.37 (0.78-2.28)	0.256		
Peripheral vascular diseases	0.43 (0.07-1.39)	0.253		
History of stroke	1.25 (0.60-2.34)	0.506		
Valvular heart disease	1.31 (0.70- 2.25)	0.364		
Renal diseases	1.19 (0.63-2.08)	0.570		
Cerebrovascular disease	0.42 (0.07-1.36)	0.329		
Prior bleeding	3.72 (1.38-8.52)	0.004	3.25 (1.12-8.19)	0.019

Factors		Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p–value
Discharge anti-thrombotic	Warfarin	3.02 (2.03-4.58)	< 0.001	2.47 (1.46-4.41)	0.001
	DOAC	0.98 (0.58-1.58)	0.946		
	APT	0.40 (0.24-0.64)	< 0.001	0.78 (0.40-1.51)	0.454
	Multiple antithrombotic[¥]	3.11 (2.11-4.57)	< 0.001	2.45 (1.61-3.71)	< 0.001

Abbreviations: OR, odds ratio; CI, confidence interval; CCI, Charlson comorbidity index; DOAC, direct oral anticoagulant; APT, antiplatelet. ***** Includes current and ex-smokers. [¥] Include OAC-APT combination and dual-APT therapy.

6.4.3 Bleeding incidence rates among treatment groups

A total of 942 patients newly initiated on antithrombotic therapy (warfarin = 431, DOAC = 258, APT = 253) contributed 1,880 patient-years (PY) of on-treatment follow-up. Mean follow-up durations by treatment category were 922 PY for warfarin, 462 PY for DOACs, and 496 PY for APT agents. Fifty-eight patients experienced bleeding events; approximately one-third of the bleeding events in the warfarin cohort (n = 13; 34.2%) and half of the events in the DOAC (n = 7; 50%) and APT (n = 3; 50%) cohorts occurred within 90 days of initiating therapy. The rates of bleeding, classified by severity and site of bleeding, are shown in Table 19. The combined rate of major and minor bleeding was higher in patients initiated on warfarin (rate, 95% CI, 4.1 [2.9 - 5.7] per 100 PY) than those prescribed a DOAC (3.0 [1.7 - 5.2]) or APT agent (1.2 [0.5 - 2.7], p = 0.002).

When bleeding events were analysed by severity, the rate of major bleeding was significantly higher in patients who commenced warfarin compared to those who commenced a DOAC or APT agent (2.4 [1.5 - 3.7] vs 0.4 [0.1 - 1.7] and 0.6 [0.2 - 1.9], respectively; p = 0.001). The rate of minor bleeding, however, was non-significantly higher in the DOAC group compared to the warfarin and APT cohorts. Comparison by bleeding site showed both ICH and upper GI bleeding rates were higher in patients initiated on warfarin than both the DOAC- and APT-treated patients. The Kaplan-Meier curves comparing event-free rates between antithrombotic therapies are shown in Figure 11. By the end of the study period, event-free rates for combined bleeding events were significantly higher in patients initiated on DOACs than in patients initiated on warfarin (log-rank p = 0.03). Similarly, event-free rates of patients initiated on APT agents were significantly higher compared to those initiated on OAC therapy (long-rank p = 0.002).

Table 19. Bleeding and mortality incidence rates per 100 patient years by treatment category.

Characteristics		Warfarin (n = 431)		DOAC (n = 258)		APT (n = 253)		
		Number	Rate per 100 PY (95% CI)	Number	Rate per 100 PY (95% CI)	Number	Rate per 100 PY (95% CI)	p-value
All bleeding events during follow-up		38	4.1 (2.9 – 5.7)	14	3.0 (1.7 – 5.2)	6	1.2 (0.5 – 2.7)	0.002
Early bleeding (within 90 days)		13	13.4 (7.6 – 22.2)	7	11.9 (5.3 – 23.5)	3	5.1 (1.3 – 15.1)	0.310
Bleeding by severity	Major (fatal + non-fatal)	22	2.4 (1.5 – 3.7)	2	0.4 (0.1 – 1.7)	3	0.6 (0.2 – 1.9)	0.001
	Minor bleeding	16	1.6 (1.03 – 2.9)	12	2.6 (1.4 – 4.6)	4	0.8 (0.3 – 2.2)	0.137
Bleeding by site	ICH	8	0.9 (0.4 – 1.8)	2	0.4 (0.1 – 1.7)	2	0.4 (0.1 – 1.6)	0.031
	Upper GI	13	1.3 (0.7 – 2.3)	2	0.4 (0.1 – 1.7)	2	0.4 (0.1 – 1.6)	0.043
	Lower GI and PR	4	0.4 (0.1 – 1.2)	2	0.4 (0.1 – 1.7)	2	0.4 (0.1 – 1.6)	0.971
	Other sites *	13	1.4 (0.8 – 2.5)	8	1.7 (0.8 – 3.5)	0	-	0.782

Characteristics		Warfarin (n = 431)		DOAC (n = 258)		APT (n = 253)		
		Number	Rate per 100 PY (95% CI)	Number	Rate per 100 PY (95% CI)	Number	Rate per 100 PY (95% CI)	p-value
Death	All-cause mortality	28	3.0 (2.1 – 4.4)	10	2.2 (1.1 – 4.1)	16	3.2 (1.9 – 5.3)	0.321
	Cardiovascular death[¥]	14	1.5 (0.9 – 2.6)	2	0.4 (0.1 – 1.7)	9	1.8 (0.9 – 3.5)	0.086
	Death due to bleeding	5	0.5 (0.2 – 1.3)	0	-	2	0.4 (0.1 – 1.6)	0.937
	Death due to other causes	14	1.5 (0.9 – 2.6)	8	1.7 (0.9 – 3.9)	7	1.4 (0.6 – 3.0)	0.939

Abbreviations: DOAC, direct oral anticoagulant; APT, antiplatelet; PY, patient years; ICH, intracranial haemorrhage; GI, gastrointestinal; PR, per-rectal.

* Epistaxis, hematuria, hematoma. [¥] Includes death due to cardiovascular diseases including fatal bleeding.

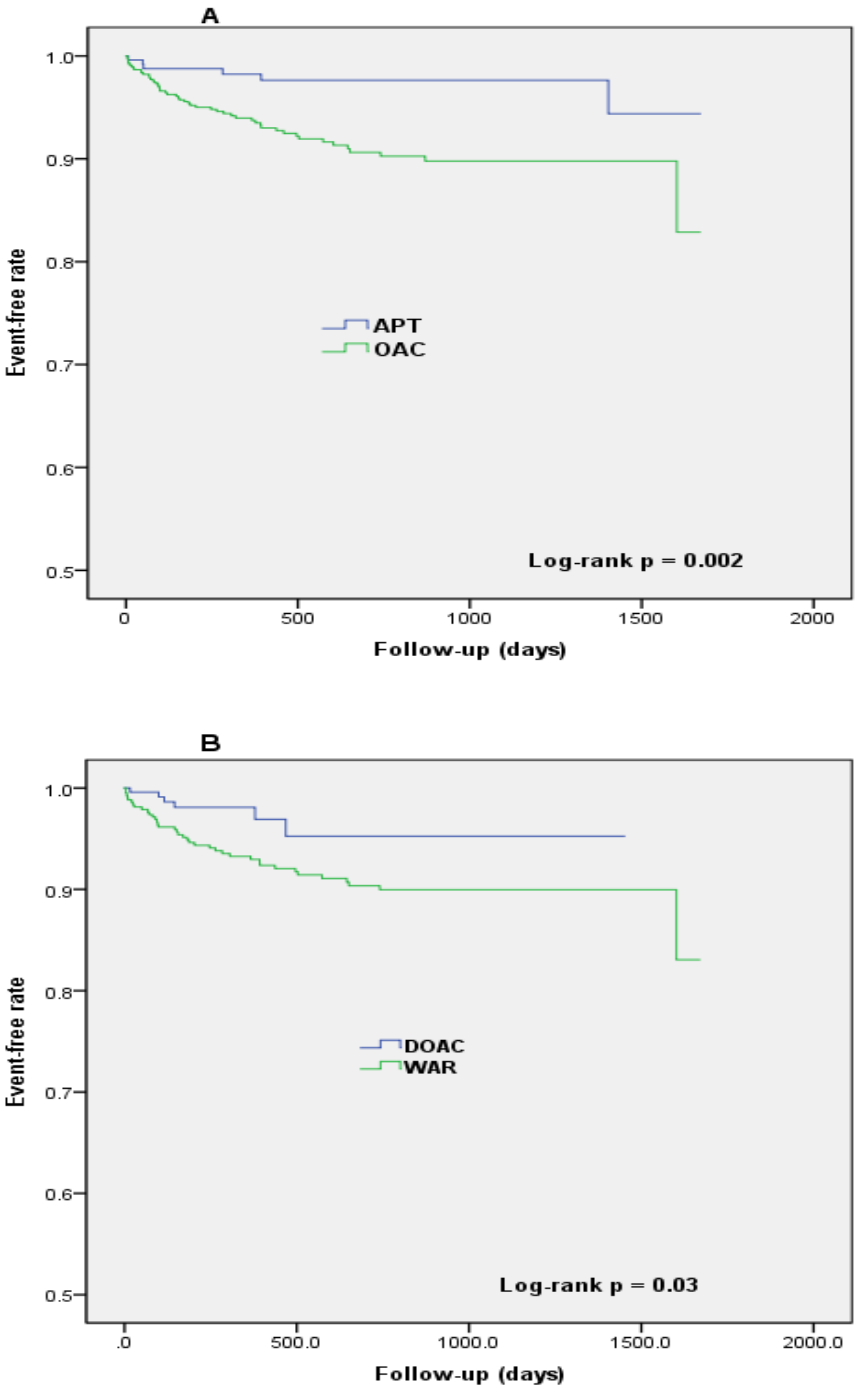


Figure 11. Kaplan–Meir curves for all bleeding events among patients newly initiated on antithrombotic therapy.

A) APT vs OAC; B) Warfarin vs DOACs. Abbreviations: APT, antiplatelet agents; DOAC, direct oral anticoagulants; OAC, oral anticoagulants; WAR, warfarin.

6.5 Discussion

In this analysis from the TAF study, we investigated bleeding events and factors associated with bleeding in patients with AF receiving antithrombotic therapy. This is one of the first follow-up studies involving a relatively large study population over an extended follow-up period featuring the introduction of DOACs into the Australian clinical setting. Both major and minor bleeding rates in this cohort were relatively low, especially in the DOAC-treated patients, while the rates of major bleeding, including ICH, in the DOAC and APT groups were lower than rates in the warfarin-treated patients. Increasing age, a history of prior bleeding, warfarin, and multiple antithrombotic therapy were independent predictors of bleeding.

The combined, major, and minor bleeding incidence rates in this cohort were lower than in similar observational studies from other countries. Early bleeding rates, however, were considerably higher than bleeding rates for the entire follow-up period. The high early bleeding incidence rate in our study was consistent with other studies which reported higher rates of bleeding soon after initiating treatment than at the later stages of therapy [89,92]. This could be explained by the complexity of treatment initiation, poor understanding of instructions, inappropriate dosing, and fluctuations in the international normalised ratio (INR) values at the earlier stages of antithrombotic therapy in AF.

Our data indicated higher major and combined bleeding rates among patients who received warfarin compared to those receiving DOAC and APT therapies. This variation was observed in the absence of significant differences in patient characteristics between patients prescribed warfarin or a DOAC (supplementary Table 20). We also noted more frequent major bleeding than minor bleeding events in the warfarin cohort. This was in contrast to findings from other

observational studies that showed more frequent minor bleeding than major bleeding events [332]. Conversely, minor bleeding events were more frequent in the DOAC-treated patients. Moreover, the rate of minor bleeding among patients initiated on DOACs was numerically higher than the rates in their warfarin- and APT-treated counterparts. Challenges in relation to the quality of anticoagulation with warfarin therapy, including suboptimal adherence, poor INR control, and interactions with drugs or food, could be among the potential reasons for the higher rate of major bleeding events observed in the warfarin-treated patients.

The rates of bleeding in patients with AF receiving antithrombotic therapy vary widely in published studies. These differences may be the result of several factors including variations in study designs, patient populations and the quality of patient monitoring. Our estimate of the major bleeding incidence rate in the warfarin initiators (2.4 per 100 PY) was lower than other observational studies, which reported major bleeding rates in warfarin-treated patients in the range of 3-8% per 100 PY [215,318,338]. Conversely, the rate of major bleeding in this study corresponded well to the rates observed in randomised trials of warfarin therapy, which have ranged between 1-3% per 100 PY [99,100,339]. This contrasted with results from most observational studies that showed substantially higher bleeding incidence rates than observed in the clinical trials. The rate of major bleeding in the DOAC group was also lower than the rates reported from both observational and trial studies of 0.5-3.6% per 100 PY [99,340,341]. Our study population included hospitalised patients. Patients with minor bleeding managed by local general practices and major bleeding leading to pre-hospital death were not included in this study, and this is the possible explanation for the lower rates of bleeding events observed.

One of the most feared complications of OAC in AF is ICH, particularly haemorrhagic stroke. In this study, the rate of ICH in the warfarin cohort was higher than the ICH rate observed in

randomised trial and large observational studies (0.9 vs 0.3-0.6 per 100 PY) [99,100,114]. The high ICH rate was probably due to the high use of combination warfarin-APT therapy. Further studies should investigate the appropriateness and clinical outcomes of using multiple antithrombotic therapies in AF. Conversely, the rate of ICH in the DOAC-treated patients was less than half the rate in patients who received warfarin (0.4 vs 0.9 per 100 PY, respectively). This corroborates other studies that showed a 50% reduction in the risk of ICH using DOACs in preference to warfarin in AF [342,343]. A meta-analysis of studies that evaluated DOACs for stroke prevention in NVAF also estimated a >50% relative reduction in the pooled incidence rate of ICH in the DOAC- vs warfarin-treated patients [102]. Few studies from clinical practice showed more frequent gastrointestinal (GI) bleeding in patients using DOACs than warfarin [332,344]. By contrast, upper GI bleeding rates were slightly higher in the warfarin than the rates in the DOAC and APT cohorts of our study.

In summary, the relatively low bleeding incidence rates observed in our study, and the heterogeneity of bleeding rates reported from other studies could reflect variability in the standard of care, methodological differences, and variations in data sources.

Identifying factors associated with bleeding is clinically important because interventions focused on modifiable factors may maximise the net therapeutic benefit of OAC therapy in patients with AF. After adjusting for differences in patient characteristics, we identified advanced age, a history of prior bleeding, treatment using warfarin (vs DOACs and APT therapy), and multiple antithrombotic (vs a single antithrombotic) as independent predictors of bleeding. Our results are consistent with other studies that examined factors associated with antithrombotic-associated bleeding in AF [244,345,346]. Some studies have identified female sex, a history of stroke, hypertension, and smoking or alcohol use as predictors of bleeding in

AF [347-349]. However, these variables were not significantly associated with bleeding in our study.

Based on these findings, bleeding events in AF could be reduced by cautious use of OACs in elderly patients, closer monitoring of OAC therapy especially in patients with bleeding history, and avoiding OAC-APT therapy in AF where possible. Although we did not assess the appropriateness of antithrombotic prescribing in this study, our data revealed a relatively high proportion of patients being prescribed OAC-APT therapy prior to their bleeding-related admission. Data from the ORBIT-AF study showed that aspirin was often used with warfarin in AF without a clear indication for APT therapy [350]. However, OAC-APT combination therapy substantially increased the risk of bleeding without a net therapeutic benefit in reducing stroke.

Our data also reinforce the safety of the DOACs relative to warfarin in terms of bleeding in general and ICH. Because DOACs have been shown to be relatively safer and more convenient than warfarin, they are recommended as first-line therapy in the contemporary European and Canadian guidelines for the management of AF [9,19]. Our data supports international findings and suggests that Australian guidelines could be revised with a clear recommendation to use DOACs as a first-line therapy for the majority of patients with NVAF. However, precaution should be taken while initiating DOACs in elderly AF patients with impaired renal function.

This study has certain limitations. We assessed bleeding resulting in hospitalisation, and data regarding minor bleeding events managed in primary care or severe events leading to pre-hospital death were not available. As a result, the rate of bleeding observed in our study may be an underestimate. However, the RHH is the largest referral centre in the region, and most patients requiring admission will be readmitted to the RHH. Our hospitalised population might

also have contributed to the higher rate of major than minor bleeding events, and for the high rate of ICH in the warfarin-treated patients. In addition, we did not investigate INR at presentation or time in the therapeutic range that could have an important role in warfarin-related bleeding events. Furthermore, we did not determine bleeding incidence rates for individual DOACs due to the small numbers of patients initiated on each of the three DOACs. Finally, this study has the limitations of a retrospective study design and can be affected by missing values or incomplete documentations. Although statistical adjustments were used, we cannot rule out unmeasured or residual confounding in the multivariate analysis.

6.6 Conclusion

Our data indicated low overall and major bleeding incidence rates, particularly among DOAC-treated patients. Increasing age, a history of prior bleeding, treatment using warfarin, and multiple antithrombotic therapy were independently associated with bleeding-related hospitalisation. These findings suggest that using DOACs in preference to warfarin and avoiding multiple antithrombotic therapies, especially in the elderly patients with AF, have the potential to reduce bleeding rates. Additional large-scale studies in the Australian clinical setting regarding comparative safety among the three DOACs, appropriateness of multiple antithrombotic therapies in AF, and associated clinical outcomes are warranted.

Table 20 (Supplementary). Baseline characteristics by newly initiated antithrombotic.

Characteristics		Warfarin (n = 431)	DOAC (n = 258)	APT (n = 253)	p-value
Demographics	Age, mean (SD)	74.6 (10.1)	72.9 (10.5)	73.1 (13.1)	0.074
	Sex, females, n (%)	178 (41.2)	124 (48.1)	106 (41.9)	0.082
	Smoking*, n (%)	180 (41.7)	95 (36.8)	89 (35.2)	< 0.001
	Alcohol (>8 units/week)	29 (6.7)	18 (6.9)	23 (9.1)	0.4966
Comorbidities n (%)	Hypertension	290 (67.3)	165 (63.9)	146 (57.7)	0.042
	Ischaemic heart disease	139 (32.2)	55 (21.3)	68 (26.9)	0.072
	Diabetes mellitus	100 (23.2)	52 (20.2)	45 (17.8)	0.229
	Congestive heart failure	67 (15.5)	42 (16.3)	32 (12.6)	0.465
	Myocardial infarction	56 (13.0)	24 (9.3)	21 (8.3)	0.3185
	Valvular heart disease	42 (9.7)	13 (5.0)	12 (4.7)	0.015
	Renal diseases	37 (8.6)	14 (5.4)	21 (8.3)	0.287
	History of stroke	32 (7.4)	22 (8.5)	9 (3.6)	0.049
	Cerebrovascular disease	19 (4.4)	4 (1.5)	5 (2.0)	0.056

Characteristics		Warfarin (n = 431)	DOAC (n = 258)	APT (n = 253)	p-value
	History of bleeding	7 (1.6)	2 (0.8)	5 (2.0)	0.511
	PVD	18 (4.2)	4 (1.5)	5 (2.0)	0.083
	CCI, mean (SD)	4.5 (1.9)	4.0 (2.2)	4.0 (2.4)	0.003
	CHA_2DS_2-VASc, mean (SD)	3.3 (1.4)	3.1 (1.6)	2.8 (1.5)	< 0.001
	HAS-BLED, mean (SD)	2.3 (0.7)	2.2 (0.7)	2.2 (0.7)	0.348

Abbreviations: CCI, Charlson comorbidity index; PVD, peripheral vascular diseases; SD, standard deviation; * Includes current and ex-smokers.

CHAPTER SEVEN

7. General discussion and conclusions

This thesis comprises a series of analyses addressing detailed investigations of antithrombotic therapy in contemporary patients with AF. Thromboprophylaxis is essential in the management of patients with AF, and effective stroke prevention can be achieved by optimal utilisation of OACs. For more than 60 years, VKAs such as warfarin were the only OAC agents available for stroke prevention in AF. Despite guideline recommendations, VKAs were often underused for stroke prevention in AF. The recent availability of DOACs as alternative agents to VKAs was anticipated to improve suboptimal use of OACs and clinical outcomes in patients with AF. The development and approval of DOACs heralded a new era for stroke prevention in AF and other embolic diseases. The four innovative RCTs have established that DOACs have similar efficacy, with superior safety profiles, compared to warfarin [98-101]. Given their multiple benefits over warfarin mainly with regard to safety and convenience, DOAC prescribing in AF was expected to grow with a profound impact in reducing suboptimal anticoagulation practices.

Limited data was available from the Australian perspective regarding contemporary patterns of overall antithrombotic prescribing and clinical integration of DOACs for stroke prevention in AF. Moreover, it was not previously known if the introduction of DOACs would help to improve suboptimal anticoagulation practices in patients with AF and have positive impacts on clinical outcomes. Thus the TAFs was launched in 2011 to enhance understanding of evolving changes in stroke prevention in AF, and help in defining future treatment strategies that may influence clinical outcomes. The TAFs was among the first Australian studies to provide data concerning temporal patterns of antithrombotic prescribing in AF, the impact of the widespread

availability of DOAC on anticoagulation practices, and clinical outcomes in patients with AF. In this body of work, we undertook a literature review pertaining to antithrombotic prescribing for stroke prevention in patients with AF in relation to guideline recommendations. Moreover, we investigated anticoagulation practices and clinical outcomes in Tasmanian patients with AF.

Our literature review (Chapter 2) summarises findings of some of the national and international observational AF registry studies. This review discusses pharmacological features of DOACs, contemporary anticoagulation practices, and early adoption patterns of DOACs. In addition to the positive trial results, variations in time of regulatory approval [351], lack of uniformity in the recommendations of guidelines [352], limited knowledge/experience for the new therapies [353], and marketing strategies/promotions [287] may influence uptake of DOACs. Indeed, contrasting results were evident from the various studies undertaken in our review. Early evidence (data between 2008 and 2013) suggests that slow adoption patterns with a limited impact on anticoagulation practice in AF were reported in most countries [181,230,243,354]. However, the majority of early investigations did not include study periods in which factor Xa inhibitors were largely available. More recent data, however, show profound changes in OAC prescribing in AF associated with the advent of DOACs. Since DOACs were introduced, AF guidelines have been revised [9,19], and there has been a significant increase in the overall rate of anticoagulation, primarily driven by the prescribing of DOACs [355-358]. Nevertheless, the impacts of general availability of DOACs on patient outcomes, and their role in reducing the overall burden of AF care remain to be investigated.

7.1 Antithrombotic prescribing patterns

The first study in this thesis analysed overall patterns of antithrombotic prescribing and clinical adoption of DOACs for stroke prevention in contemporary patients with AF. This analysis adds to an earlier investigation conducted during the familiarisation phase of DOACs in Australia [137], by providing a comprehensive picture of OAC utilisation patterns during a time period in which the new therapies were subsidised by the Australian government. As such, it offers broad descriptions regarding temporal patterns of antithrombotic prescribing in AF in general, and DOAC adoption trends in particular.

Our results revealed slow clinical integration of DOACs after they were approved by the TGA in 2011 until their listing on the PBS for subsidy by the government (mid-2013). Subsequently, rapid growth in the use of DOACs was noted soon after their listing on the PBS, with the main increase being driven by prescribing of apixaban and rivaroxaban. During the last quarter of this study, apixaban became the most commonly prescribed DOAC followed by rivaroxaban, while dabigatran prescribing remained stable at low proportions. This study also identified a progressive decline in the prescribing of APT therapy for stroke prevention in AF through time. The decreasing trend in APT prescribing may be driven in part by the widespread availability of DOACs, but also by the increasing realisation that APT agents are barely effective compared to OAC therapy [105,359,360]. Overall, this study showed a paradigm shift in the prescribing patterns of antithrombotic therapy for the prevention of thrombosis in AF over time. The new anticoagulants were broadly adopted, becoming more frequently prescribed than warfarin and APT therapies soon after they were listed on the Australian PBS.

Having observed that DOACs have been largely integrated for stroke prevention in AF, the second analysis in this section focused on investigating whether the availability of DOACs has increased the proportion of AF patients receiving guideline-recommended OAC therapy. We observed a significant increase in the proportion of patients with AF receiving OAC treatment in the post-DOAC compared to the pre-DOAC era; most importantly, anticoagulation of high-risk patients with AF improved significantly in the post-DOAC era (55.2% vs 63.1%, $p<0.001$). This change was driven primarily by the increase in prescribing of DOACs. Indeed, our multiple regression analysis revealed DOAC availability (post-DOAC era) was an independent predictor of OAC prescribing, resulting in an approximately 40% increase in the odds of a patient being prescribed an OAC. Similar to our data, the introduction of DOACs in real-world practice was associated with improved rates of overall OAC use in the PINNACLE AF-registry data involving 655,000 patients with NVAF [361].

The rate of OAC prescribing in AF varies widely depending on countries, study settings and study populations, ranging between 30% and 90% [95,362]. Overall, most observational data reported increasing trends of OAC prescribing in AF associated with the advent of DOACs. The GARFIELD-AF study showed temporal changes in the prescribing of antithrombotic therapy in AF in five sequential cohorts between 2010 and 2015. The rate of OAC prescribing increased from 54.7% in cohort-2 to 73.9% in cohort-5. The increase in OAC prescribing in this study was shown to be primarily driven by DOAC prescribing [357]. Similarly, data from GLORIA-AF, phase-2, revealed a significant increase in OAC prescribing after the introduction of DOACs [286]. Compared to the anticoagulation rate in the pre-DOAC era, the anticoagulation rate in the post-DOAC era markedly increased (from 64% to 80%, with DOAC prescribing greater than VKA prescribing overall).

This study also explored important factors associated with OAC prescribing in AF. The general availability of DOACs was identified as a significant positive predictor of OAC prescribing in this study population. Conversely, increasing age, female sex, and a history of prior bleeding were inversely associated with OAC prescribing. Advanced age (especially over the age of 80 years), falls risk, prior bleeding, and perceived high risk of bleeding on anticoagulation have been identified as common barriers to OAC prescribing in AF [20,363]. However, the risk of stroke without any OAC often exceeds the bleeding risk on anticoagulation, even in the elderly patients, including those with frequent falls and frailty [298,364].On the other hand, the risk of bleeding on APT treatment, commonly prescribed in elderly AF patients, is not different to the bleeding risk on warfarin or DOAC treatment [365,366]. Accordingly, increasing age and associated frailty should not deter OAC prescribing in patients with AF. Overall, this analysis showed the clinical introduction of DOACs was associated with a significant increase in the rate of OAC prescribing in AF, but substantial gaps remain requiring further improvement.

7.2 Clinical outcomes

While the global burden of AF has increased in recent decades, the management of AF has also greatly evolved. The major advances pertaining to stroke prevention in AF include: the clinical introduction of DOACs, updates in treatment guidelines and stroke risk scoring methods, and associated increase in OAC prescribing practices [361]. These changes have been anticipated to bring about improvements in patient outcomes by reducing thromboembolism and all-cause mortality. However, inconsistent data has been reported regarding time-trends of TEs and all-cause mortality in patients with AF. Some studies have shown declining rates in AF-related stroke and mortality in the population [28,307,367], while more recent data indicated a limited reduction in the risk of AF-related TEs over time [368,369].

Comparative studies about TEs and all-cause mortality between pre- and post-DOAC approval periods in the Australian AF population are limited. Our data from the preceding two analyses (Chapters 3 and 4) showed a major shift towards using DOACs, and a significant increase in the rate of OAC prescribing in AF. These results raised the critical question of whether the risk of TEs and all-cause mortality in AF had improved during the post-DOAC era. The subsequent analysis (described in Chapter 5) was a follow-up study that examined possible implications of the observed treatment changes by comparing clinical outcomes in two time-periods: prior to and following the general availability of DOACs in Australia.

Interesting results emerged from this analysis suggesting a profound decline in the rates of TEs and all-cause mortality in the later than in the prior cohort. This was despite broad similarities in baseline demography, comorbidities, and stroke risk scores between the two cohorts. Given the increased morbidity and mortality associated with suboptimal anticoagulation in AF [370], the improved patient outcomes observed post-DOAC availability in our study are noteworthy. Increased DOAC prescribing in preference to warfarin, improved relative safety and efficacy of DOACs, and increased anticoagulation rates are among the likely explanations for the improved patient outcomes observed in this study. Indeed, our Cox-regression analysis showed hospitalisation post-DOAC availability was associated with a significant decrease in the risk of TEs. Our findings, however, should be interpreted with caution; although this study showed a reduction in the rates of TEs and all-cause mortality in the later study period, this data does not fully explain the reasons for the declining trends. Patient outcome in the real-world practice is a multifaceted issue that can be influenced by several confounding factors. Hence, neither the increase in prescribing of DOACs nor the increase in anticoagulation rates fully accounts for the reduction in TEs and all-cause mortality.

Bleeding is a major challenge and the most common ADR of antithrombotic therapy in AF. Major bleeding events such as ICHs are the most devastating complications of anticoagulation associated with significant morbidity and mortality [331,371,372]. Thus, reducing major bleeding represents an important step in improving the net clinical benefit of OAC treatment in AF. Understanding of rates and risk factors for bleeding in contemporary patients with AF receiving antithrombotic medications is essential in planning future research and designing management strategies tailored to individual patients. Furthermore, data pertaining bleeding-related hospitalisation during antithrombotic treatment is important in light of the increased prescribing of DOACs for stroke prevention in NVAF. The last analysis in this thesis assessed bleeding incidence rates and identified factors associated with bleeding in patients with AF receiving warfarin, DOACs, and APT agents.

The overall rates of bleeding in this cohort were low relative to similar observational data. Our study population involved hospitalised patients; patients with minor bleeds managed in general practice or those with severe bleeds leading to pre-hospital death were not included. This may be a potential explanation for the low rates of bleeding events in this study. The rate of ICH in warfarin-treated patients, however, was higher than rates reported from observational and trial data (0.9 vs 0.3-0.6 per 100 PY) [99,100,105,114]. Conversely, DOAC-treated patients had a lower rate of ICH than warfarin-treated patients (0.4% vs 0.9% PY). This was in agreement with other findings that showed a 50% reduction in the risk of ICH using DOACs in preference to warfarin therapy in AF [102,342]. Increasing age, history of prior bleeding, treatment using warfarin, and multiple antithrombotic therapies were significantly associated with bleeding events. Although we did not assess the appropriateness of multiple antithrombotic treatment in this study, our data revealed a relatively large proportion (34%) of AF patients being prescribed

OAC-APT or dual-APT treatment prior to their bleeding-related hospital admissions. Multiple antithrombotic use is not uncommon in AF, though largely inappropriate, and explained by coexistence of coronary artery diseases. Data from the ORBIT-AF registry study also showed that aspirin was used with warfarin in about 40% AF patients without a clear indication [373]. However, antithrombotic combination substantially increases the risk of bleeding without a net benefit in reducing the risk of stroke [350]. Further studies are required to investigate the appropriateness and outcomes of multiple antithrombotic prescribing in patients with AF.

7.3 Practice implications

This study has several implications for clinical practice. Although a significant increase in OAC prescribing in AF was observed, substantial gaps remain requiring further improvement. Our data showed suboptimal adherence to guideline recommendations; a large proportion of low-risk patients received OAC therapy, whereas a considerable percentage of patients with a Class I indication for anticoagulation received APT agents or were discharged without any antithrombotic therapy. Despite regional and other differences, patients with AF worldwide demonstrate broadly similar risk profiles and suffer a significant burden of cardiovascular disease [356]. The prescribing of DOACs and the overall use of OACs in AF are increasing worldwide, with a concomitant decrease in the prescribing of VKAs and APT agents. However, international patterns of stroke prevention in AF vary widely. The rate of OAC prescribing in our study was lower than rates reported in Europe [176,278], whereas it was comparable to data observed from the United States of America [291]. Observational studies indicated that inadequate antithrombotic guideline adherence in AF leads to an unacceptably high number of potentially preventable strokes [374].

Defining an optimal target for OAC prescribing in AF could be challenging due to lack of global consensus on eligibility for anticoagulation, primarily in the intermediate-risk groups and frequent revision of AF treatment guidelines. Nonetheless, the net clinical benefit of OAC treatment in AF is almost universal, with the exception of patients at very low stroke risk. Thus it remains imperative to appropriately implement current guideline recommendations, and all intermediate or high-risk AF patients without contraindication to OACs should be targeted for anticoagulation.

Studies have identified a broad range of barriers to optimal OAC prescribing in AF including: knowledge gaps regarding the risk of AF-related stroke, the benefits and risks of OAC therapies in general and DOACs in particular; lack of awareness pertaining the potential use of DOACs for warfarin-unsuitable patients; lack of recognition of expanded eligibility for OAC; lack of availability of reversal agents mainly for factor Xa inhibitors and the difficulty of anticoagulant monitoring for DOACs; and concerns about the bleeding risk of anticoagulant therapy, primarily with DOACs and in the setting of OAC-APT therapy [375,376]. Thus, several strategies have been proposed to improve anticoagulation in AF including [377,378]:

- Increasing awareness about AF and the risk of AF-associated stroke, benefits and risks of OAC therapies via educational initiatives.
- Defining the role of warfarin in the DOAC era including eligibility and ineligibility for different anticoagulant agents.
- Identifying DOAC reversal agents and monitoring strategies and making knowledge regarding their use publicly available.
- Undertaking large observational studies to refine the understanding of anticoagulant utilisation patterns and patient outcomes in hospitals and community practice settings.

Our data also indicated a relative decrease in the incidence rates of TEs in the post-DOAC era. Furthermore, this study reinforced the relative safety of DOACs in terms of bleeding in general, and ICH in particular. Thus bleeding-related hospitalisation in AF can be significantly reduced by using DOACs in preference to warfarin, closer monitoring of OAC treatment especially in elderly patients and in those with a history of prior bleeding and avoiding/minimising the use of multiple antithrombotic therapies in AF where possible. Because DOACs have been shown to be safer and more convenient to use than warfarin, they are recommended as first-line agents for the prevention of stroke in NVAF in the European and Canadian AF guidelines [9,19]. Our findings support international studies and suggest that local management protocols could be developed with a clear recommendation to use the new OACs as a first-line therapy in patients with NVAF. The recently published Australian AF management guideline also recommends DOACs in preference to warfarin when initiating an OAC for stroke prevention in NVAF [118].

This study demonstrated that shifting from VKAs and APT therapies to DOACs at a population level was associated with a decline in TE and bleeding rates for patients with AF. These findings can be used by policy makers at various levels of the health care system to introduce quality improvement programs, and to develop clinical performance measures such as implementation of consistent guideline-based recommendations for stroke prevention in patients with AF. Decision makers in hospitals and general practices can also develop treatment protocols pertaining to anticoagulant selection, patient education, and follow-up programs. Moreover, our data can serve as a basis for government research departments to undertake further studies regarding the financial burden of AF-related stroke, the role of DOACs in reducing this burden, and align health care system incentives to improve access to the new OACs.

Providing evidence about patterns of stroke prevention treatment and clinical outcomes in AF is important for rational use of anticoagulant agents. Accordingly, findings of this study can be used by clinicians for choosing antithrombotic therapies in agreement with current guideline recommendations, and patients with AF for additional information regarding the various OAC options available in clinical practice. Furthermore, systematic educational interventions can be designed for health professionals to enhance the understanding of the new OACs and treatment outcomes in AF. This can help to improve adherence to guidelines for stroke management in AF. Finally, shared decision-making tools can be developed to guide care providers and increase knowledge of patients about the new therapies. A primary focus should also be to develop a greater awareness about AF and the treatment options in the primary care setting.

7.4 Limitations

This study has certain limitations. The study involved hospitalised AF patients who could be relatively more comorbid than patients managed in primary care. Hence, our data may not fully reflect OAC prescribing practices in the community setting. Moreover, this was a single centre study conducted in one referral hospital in the Southern Tasmania. However, the relatively large number of participants over an extended study period, and the centre being the largest referral hospital in the region improved the robustness and representativeness of our data. Missing values and incomplete documentation inherent to retrospective studies were additional limitations. Another limitation is that we used the CHA_2DS_2-VASc score to analyse OAC prescribing. While widely used in practice, this scoring system was not universally accepted, with some controversy in female patients with intermediate risk of stroke. Anticoagulation of 65-74 year-old women without additional clinical risk factors was debatable [379,380]. The

recent Australian and European AF guidelines do not recommend OAC in this group, and adherence to recommendations may have improved after the publication of these guidelines.

Given the observational nature of our data, the clinical outcome analyses in this study also have some limitations that should be taken into consideration. First, there is a potential for selection bias inherent to retrospective observational studies; exposure to antithrombotic therapy at index admissions was not randomised. Second, we were not able to capture TEs or bleeding events resulting in admission to other settings, minor events managed in local general practices, severe complications leading to pre-hospital death or death occurring outside our study setting. This may underestimate TE, bleeding and mortality incidence rates observed in this study. Third, as the study population involved hospitalised AF patients, incidence rates may not reflect clinical outcomes of patients with AF managed in the community setting. Finally, the increased OAC prescribing rates observed in this study may not be fully explained by the availability of DOACs; other unaccounted factors such as marketing promotion of the new OACs, the increased research focus and global conferences pertaining AF, and increased awareness about AF may have also contributed to the improved rates of anticoagulation in AF.

7.5 Conclusions

In this real-world cohort of patients with AF, antithrombotic prescribing changed significantly over the study period, characterised by a major shift towards the prescribing of DOACs. The widespread availability of DOACs has been associated with a significant increase in the rates of OAC prescribing. However, a large proportion of at-risk patients received APT treatment or remained untreated highlighting the need for further improvement. Our data also suggested that stroke and all-cause mortality rates tended to decline during the post-DOAC era, possibly

driven by the increased anticoagulation practices and the use of DOACs in preference to warfarin. Furthermore, the rate of major bleeding and ICH, in particular, was lower in DOAC- than warfarin-treated patients. We also identified several factors associated with OAC prescribing, thromboembolism and bleeding events that can be targeted for future interventions. In summary, the findings from the sequence of analyses described in this thesis offer a number of real benefits to the various stakeholders involved in the management of AF. The findings reported in this thesis could also be used to promote understanding of the various OAC options including associated risks and benefits. In Australia, where anticoagulation of patients with AF remains suboptimal and awareness of patients regarding DOAC treatment is low [381], the impacts of our findings could be significant.

7.6 Recommendations and future directions

Results from this research will aid in the development of strategies to address the suboptimal management of at-risk patients with AF. Several issues for further investigation arose from this body of work, as outlined below.

- Although there was an increase in OAC prescribing in the post-DOAC era, anticoagulation of high-risk patients in this study was lower than rates reported in recent large AF-registry data (63% vs 69% and 87% in GARFIELD-AF and ORBIT-AF II, respectively) [356]. Moreover, APT therapy was widely used among high-risk patients in both eras (38.9% and 28.2% in the pre- and post-DOAC eras, respectively). These findings highlight the need for further research to identify barriers to OAC prescribing in AF and address them accordingly.
- We have identified increasing age and prior bleeding as potent negative predictors of OAC prescribing. However, observational studies reported that bleeding risk in aging is

overestimated and should not discourage OAC prescribing in AF [141,298]. Thus, it would be worthwhile to investigate prescribers' concerns regarding OAC therapy in AF, especially in the elderly patients and in those with a history of prior bleeding.

- Prescribing OAC-APT or dual-APT therapy is common in clinical practice when patients are diagnosed with concomitant AF and coronary artery diseases. However, the safety and efficacy of using multiple antithrombotic therapies in patients with AF presenting with coronary heart diseases has always been debatable [382]. In our study, a large portion of patients hospitalised with bleeding were receiving OAC-APT or dual-APT treatment prior to their admission. Moreover, the use of multiple antithrombotics was associated with a 3-fold increase in the risk of bleeding-related hospitalisation. Yet in this analysis, appropriateness of multiple antithrombotic treatment in AF was not evaluated. Given the clinical introduction of DOACs for stroke prevention in AF, the complexity of OAC-APT combination prescribing is increasing. Nonetheless, robust studies regarding the safety and effectiveness of OAC-APT in general and DOAC-APT combinations in particular are lacking. Future studies should investigate the appropriateness and outcomes of patients with AF prescribed multiple antithrombotic therapies.
- There was a decline in the rates of TEs and all-cause mortality in AF during the post-DOAC study period relative to the pre-DOAC study period. Moreover, favourable outcomes were observed in DOAC-treated patients when compared to warfarin. However, head-to-head trials or indirect comparative analysis of the relative effectiveness and safety of individual DOACs needs larger number of participants and will be the subject of future investigations including more patients with an extended follow-up.
- Lastly, this study focused on hospitalised AF patients while the majority AF management occurs in primary care settings. Accordingly, multicentre studies involving large numbers

of Australians with AF would be prudent to review the overall impact of the availability of DOACs on anticoagulation practices in AF, time-trends of clinical outcomes, and the overall burden of AF care. Results from such studies will provide robust information in guiding decision-making in AF.

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Appendices

Appendix A. AF data collection guide

The main objectives of this project are to:

- Review overall antithrombotic prescribing patterns and clinical integration of DOACs for stroke prevention in Tasmanian patients with AF admitted to RHH between January 2011 and July 2015.
- Quantify and compare anticoagulation practices in patients with AF before and after the general availability of DOACs in Australia.
- Investigate clinical outcomes of antithrombotic treatment in AF.

Study time frame: 1 Jan 2011-30 July 2015

Inclusion criteria

- All the patients diagnosed with AF as their primary diagnosis (i.e. AF is the presenting as a chief complaint) or secondary condition (i.e. AF is listed as a current illness in the medical history or discharge summary).
- Patients with both valvular or non-valvular AF
- Age > 18 years

Exclusion criteria

- Acute episode of AF that gets settled spontaneously or upon cardioversion without documented recurrences (e.g. Episode of AF post CABG that gets reverted to SR after certain antiarrhythmic drug administration). If the patient has been discharged without any notes, follow them up with their OPD records and try to track if they are still on antithrombotic therapy (include such uncertain cases as they have been discharged on antithrombotic therapy). If there is no evidence of continuing AF, the patient should be excluded.
- Any acute AF admission due to illness/poisoning etc. that settles on its own without needing any antiarrhythmic/antithrombotic therapy.

Initial admission and readmissions

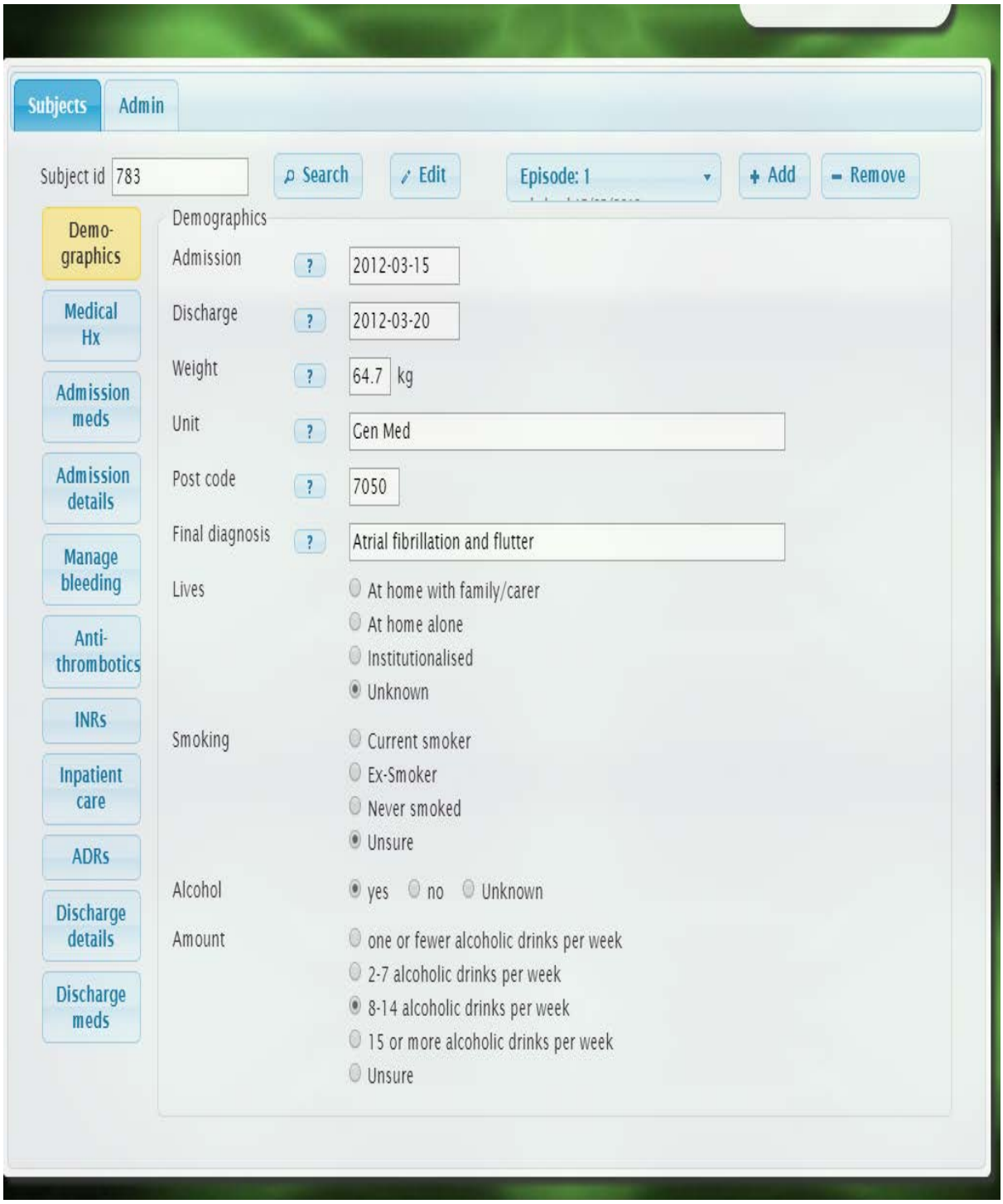
We need to look at each and every admission that falls within our time frame and **consider the earliest admission as Episode 1** (provided the patient has AF at that time **and** fulfils our inclusion criteria) and follow up all subsequent admissions as readmission regardless of the cause. Based on the **primary readmission diagnosis** enter them into the database e.g. if it was due to COPD mark it as 'none of the above' or if due to MI mark it as thromboembolism. Document the readmission as 'bleeding' only if they were receiving antithrombotic therapy at the time of the bleed; otherwise use 'none of the above.' Other readmission categories can be used regardless of whether or not the patient is receiving an antithrombotic.

Types of AF

i. Every patient who presents with AF for the first time is considered patient with **first diagnosed AF,** irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
ii. **Paroxysmal AF** is self-terminating, usually within 48 hours. Although AF paroxysms may continue for up to 7 days, the 48 hour time point is clinically important—after this the likelihood of spontaneous conversion is low and anticoagulation must be considered
iii. **Persistent AF** is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC).
iv. **Permanent AF** is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia is redesignated as 'longstanding persistent AF'. We can note down the types of AF as per the diagnosis (if mentioned) if not go through the medical progress and try to categorise it based on the definition.

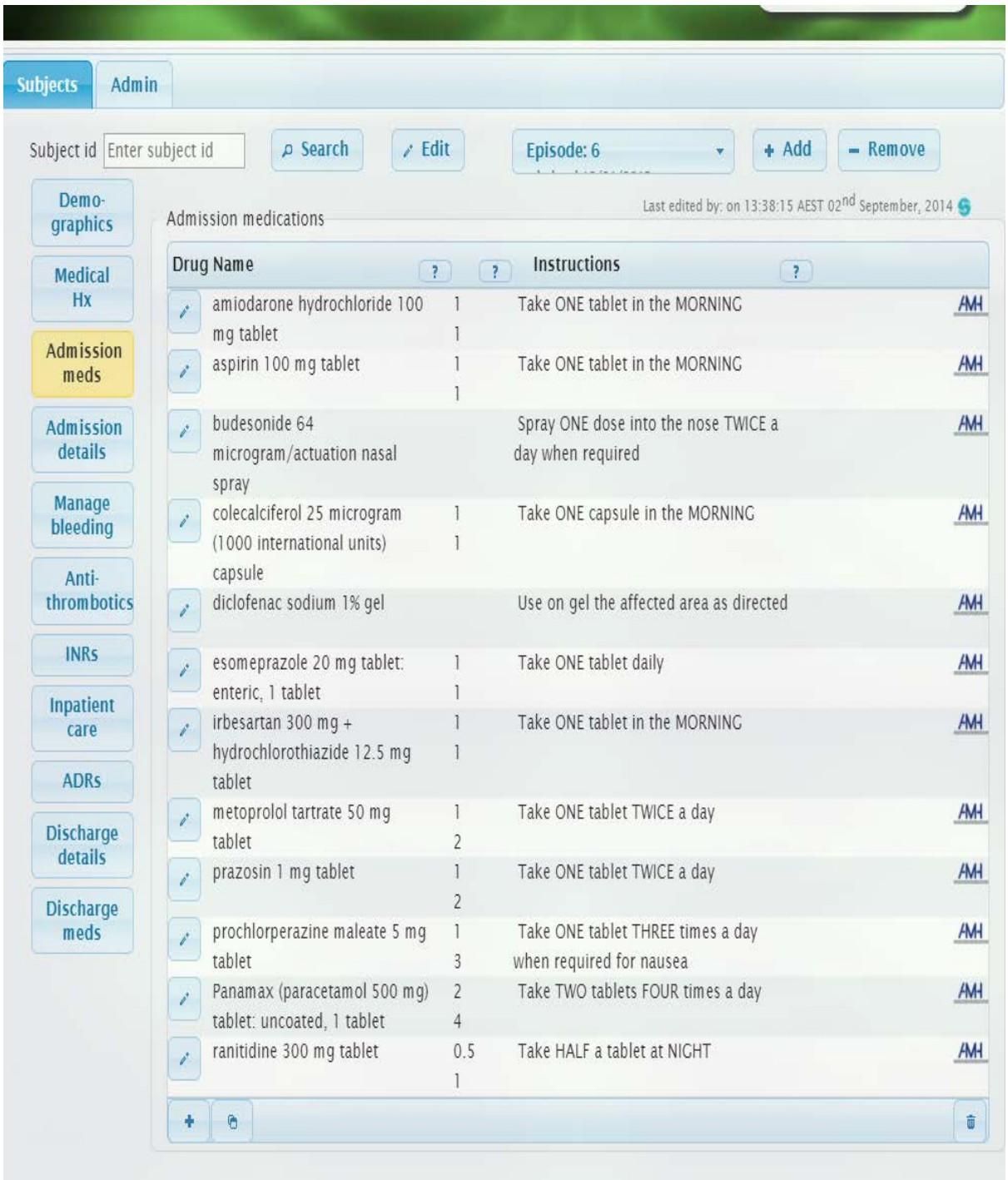
Appendix B. Data collection tools/study database

B.1. Demographics

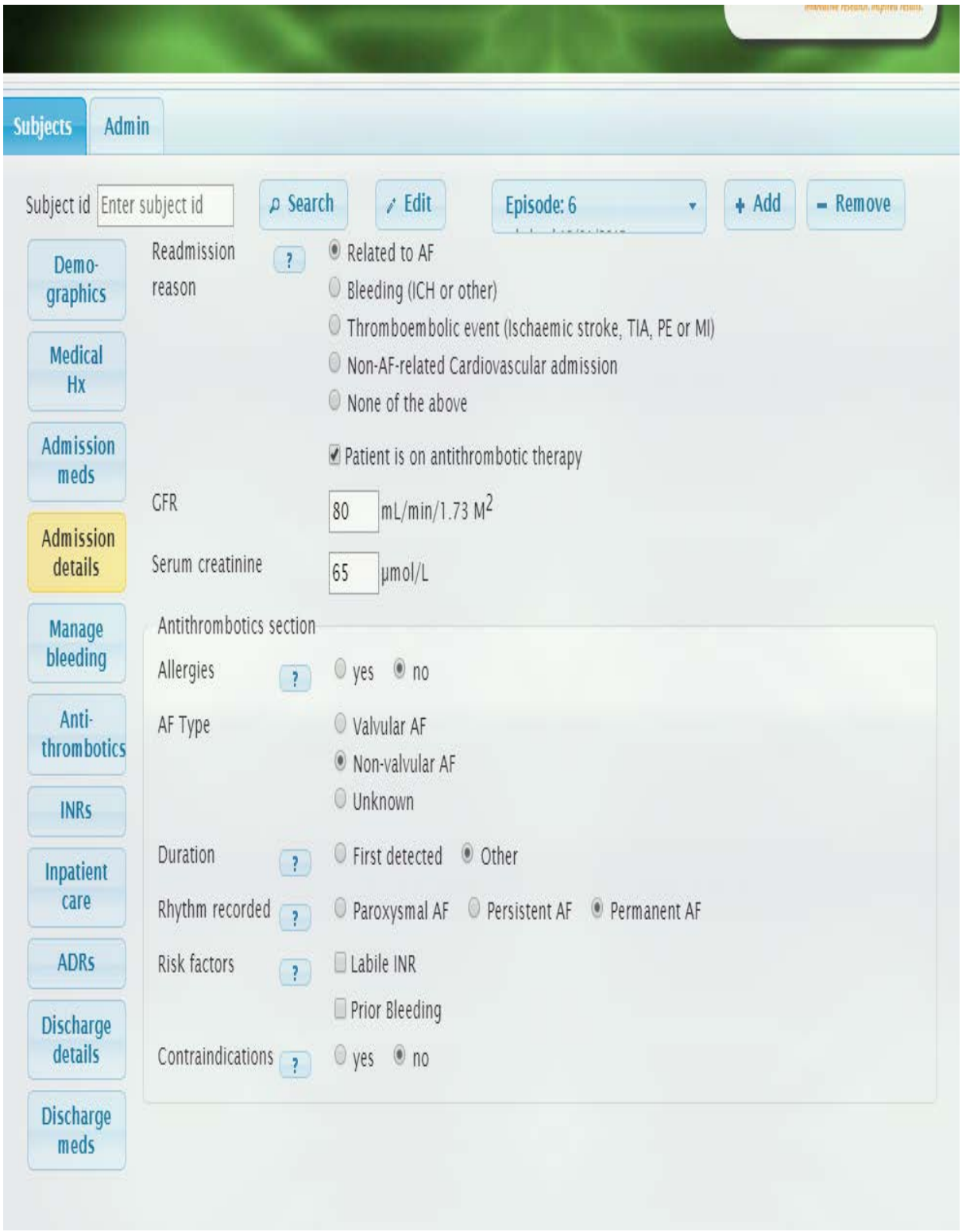


B 2. Medical history

B 3. Admission medications

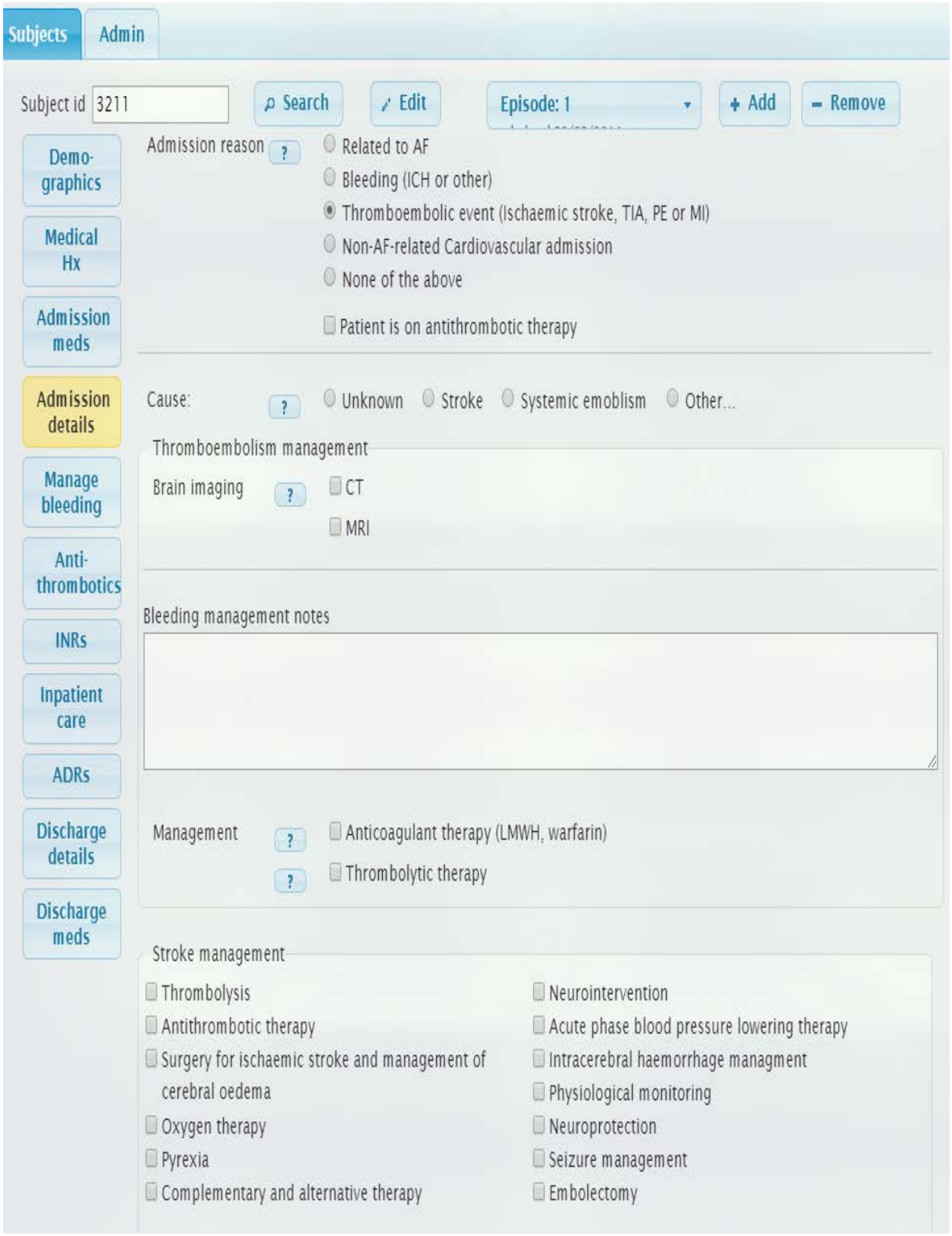


B 4. Admission details

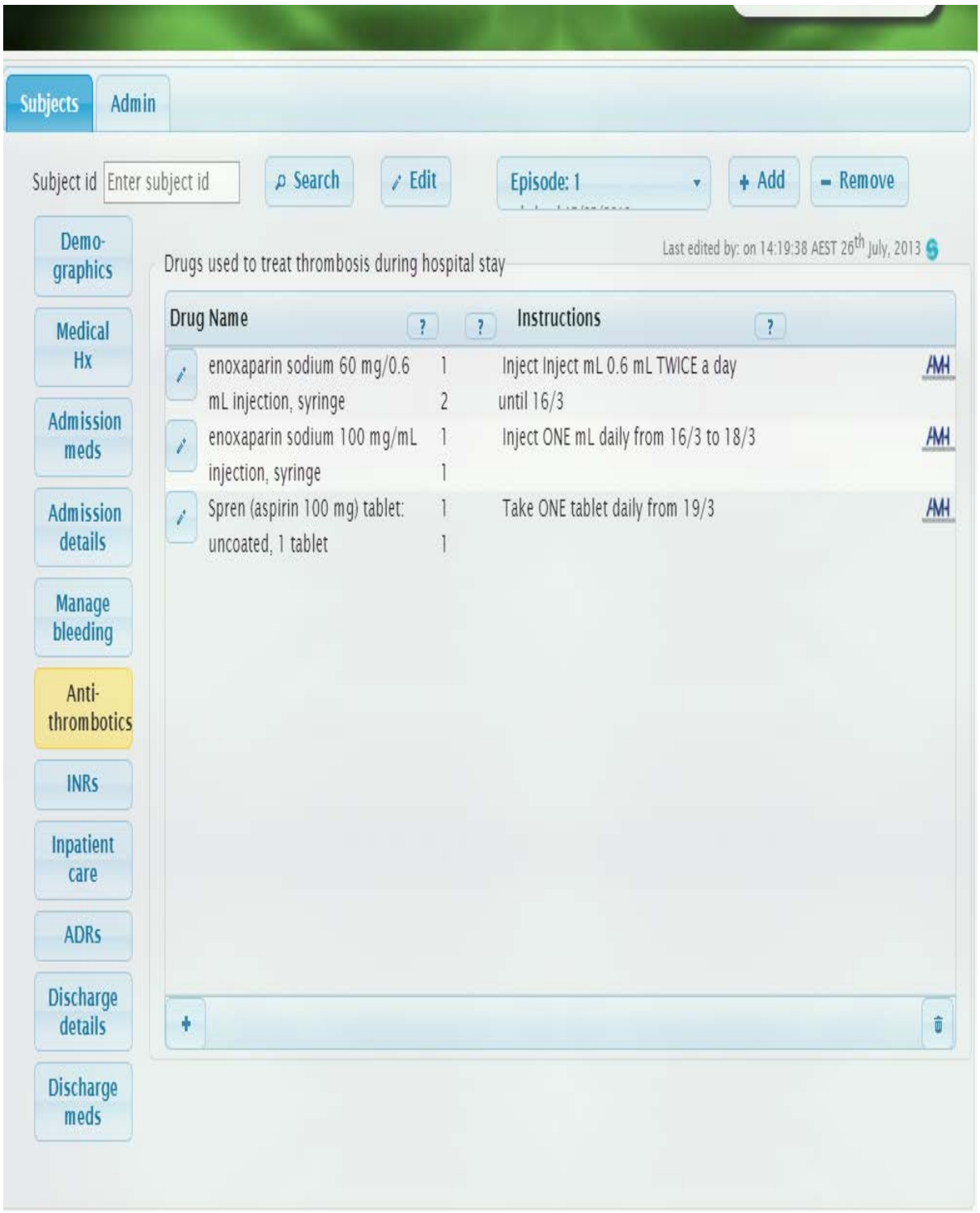


B 5. Bleeding events and management

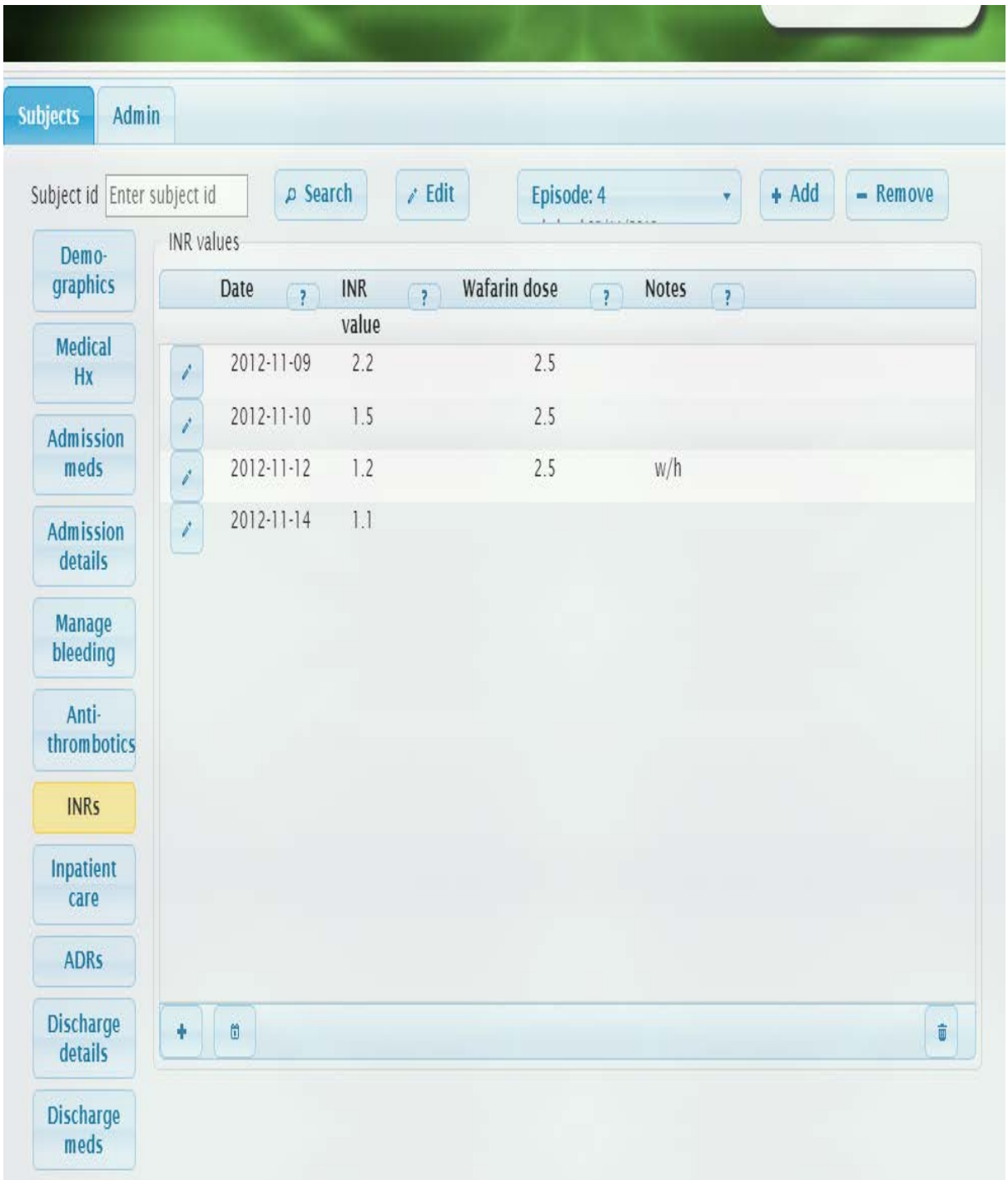
B 6. Thromboembolic events



B 6. Antithrombotics (during hospital stay)



B 6. INRs (for patients taking warfarin)



B 7. Discharge details

B 8. Discharge medications

Appendix C. Ethics amendment approval letter

Notification of Amendment Approval: H0012729 Outcomes of antithrombotic therapy in a new era: the Ta

Lauren.Black@utas.edu.au

Mon 19/01/2015 2:25 PM

To: Leanne Chalmers <leanne.chalmers@utas.edu.au>;

Cc: Luke Bereznicki <luke.bereznicki@utas.edu.au>; nicole.hancock@dhhs.tas.gov.au <nicole.hancock@dhhs.tas.gov.au>; prt@dhhs.tas.gov.au <prt@dhhs.tas.gov.au>; Durga Bista <durga.bista@utas.edu.au>; Endalkachew Alamneh <endalkachew.alamneh@utas.edu.au>; Lauren Black <lauren.dipalma@utas.edu.au>;

Dear Dr Chalmers

Ethics Ref: H0012729

Title: Outcomes of antithrombotic therapy in a new era: the Tasmanian experience

I wish to inform you that the Human Research Ethics Committee (Tasmania) Network has approved the following amendment for the above named study:

Amendment Add new Investigator - E Alamneh

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2014).

This email constitutes official approval and no hard copy notification will be sent. It is the responsibility of the first-named investigator to ensure that their co-investigators are aware of the content of the correspondence.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Kind regards

Lauren Black

--

Lauren Black

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